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JOURNAL OF NEUROSURGERY

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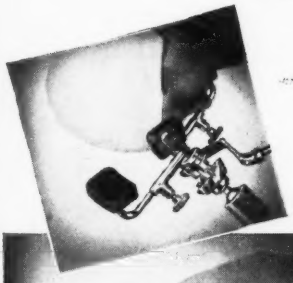

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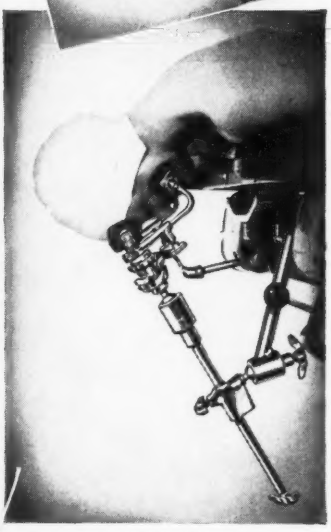

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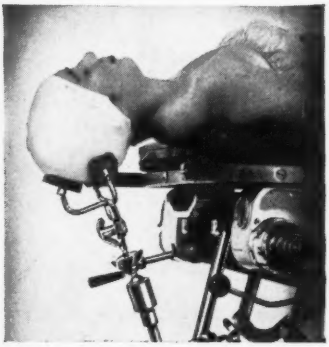

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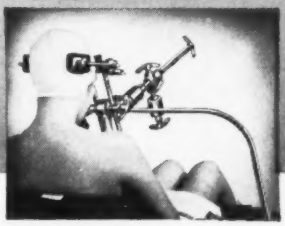

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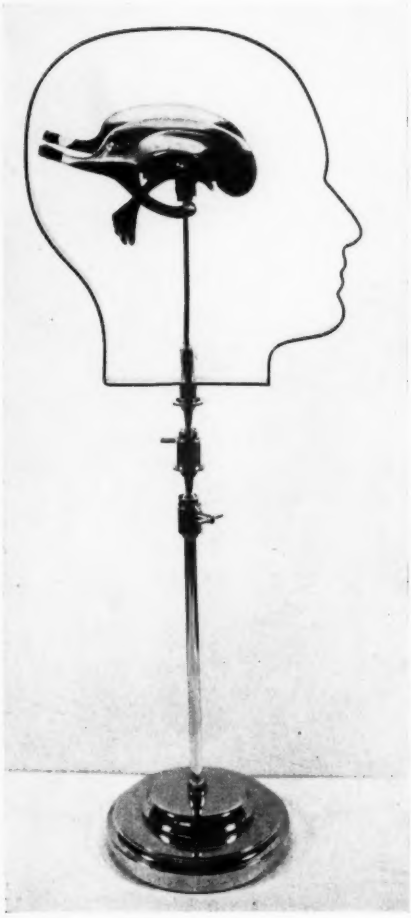

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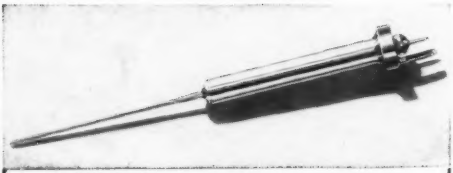

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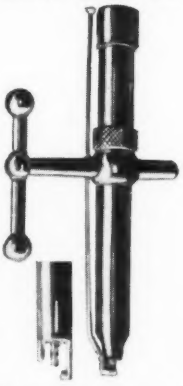

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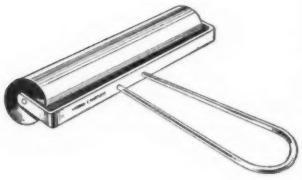

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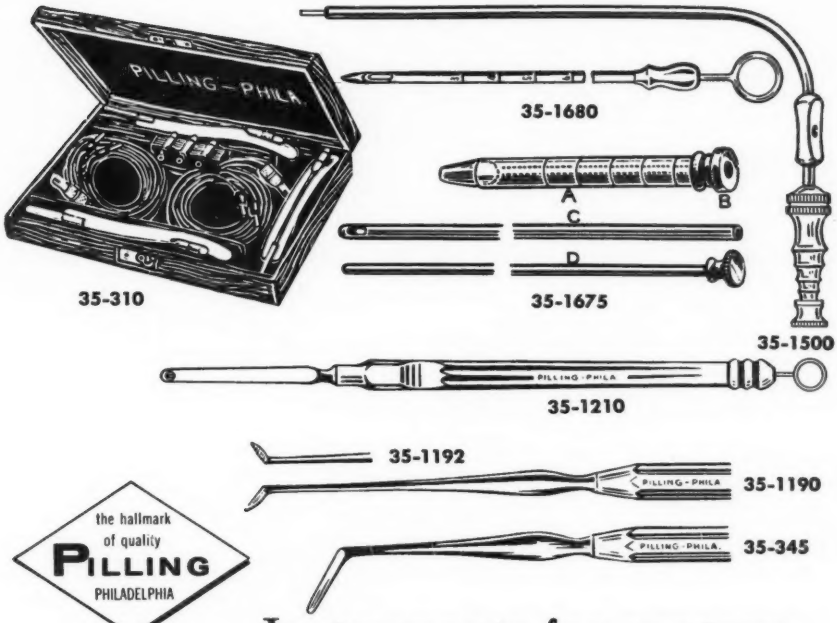

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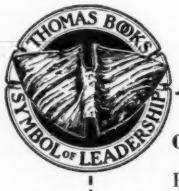

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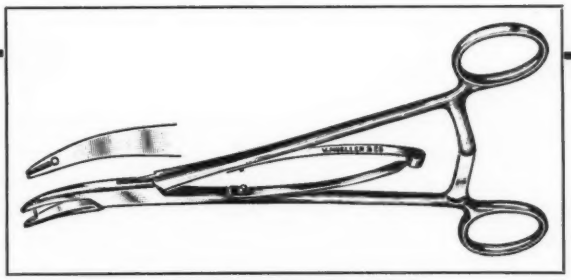

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SOME EFFECTS OF INJECTIONS OF HYALURONIDASE INTO THE SUBARACHNOID SPACE OF EXPERIMENTAL ANIMALS*

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(Received for publication February 13, 1956)

STUDIES of the influence of enzyme injections on fluid absorption, hematoma dissolution and prevention of excessive fibrosis[1] have been carried on in most areas of the body with the exception of the central nervous system. To extend such studies to this area an investigation of the effects of injecting hyaluronidase† in the subarachnoid space was undertaken.

METHOD AND MATERIALS

To test initially the influence of cerebrospinal fluid on the spreading effect of hyaluronidase in tissues, cerebrospinal fluid in 1 cc. amounts obtained from the cisterna magna of *Macacus rhesus* monkeys and cats was used to dissolve 150 turbidity reducing units of hyaluronidase. At 30-min. intervals up to 3 hours these solutions mixed with 2 cc. of 0.5 per cent methylene blue or with 100 cc. of saline were injected subcutaneously to provide a visual method of recognizing the spreading effect of the enzyme. Control injections were made simultaneously in symmetrical regions using equal quantities of the same solutions without hyaluronidase. The spreading effect of the hyaluronidase appeared to be unaltered by the cerebrospinal fluid.

A second group of animals anesthetized by intravenous pentobarbital (30 mg./kg.) were studied. Each animal was placed on its right side during the first stages of the experiment. Increments of 1500 units of hyaluronidase were dissolved in 1 cc. amounts of cerebrospinal fluid obtained from the animal being used and injected into the subarachnoid space. Pressure changes were followed for 15 minutes after returning the solution to the cisterna. This procedure was repeated until the total enzyme injected ranged from 6000–9000 units.

Small quantities of cerebrospinal fluid were withdrawn and studied for cellular reactions at the end of 2, 4, 24 and 72 hours by smears stained by Wright's technique and in some instances with supravital preparations using neutral red and Janus green. Total protein determinations were made at the end of 4, 24 and 72 hours. Alteration in the permeability of the blood-brain barrier was tested in 3 instances by injecting into the peritoneal cavity 1 gm. of trypan blue dissolved in 10 cc. of saline, and the time of appearance of the dye in the cerebrospinal fluid was noted. The 3 *Macacus rhesus* monkeys used were kept for observation for 36 hours, 1 week and 6 months. The 6 cats were sacrificed at 4 hours, 2, 5, 7, 10 and 12 days. Gross and microscopic studies were made of the brains of all the animals.

* Presented at the meeting of American Association of Anatomists, Milwaukee, Wisconsin, April 4–6, 1956.

† Hyaluronidase supplied by Wyeth Pharmaceutical Co., Philadelphia, Pa. and G. D. Searle Co., Chicago, Ill. with partial support of this project by a grant from G. D. Searle Co.

In a third group 4 cats received daily instillation of 1500 units of hyaluronidase for 4 days into the cisterna magna and 4 other cats for 8 days. Daily cerebrospinal fluid cell counts and neurological observations were made. In 2 of these animals trypan blue was injected intraperitoneally as previously described. Fourteen days following the last hyaluronidase instillation all animals were sacrificed. The vessels to the head were perfused with normal saline followed by 10 per cent formalin, and gross and microscopic studies of the brains were made.

RESULTS

All animals in the second group, which received intrathecal hyaluronidase over a short period of time, demonstrated similar responses with only slight variations in degree. Representative changes of cerebrospinal fluid pressure and cells, and alterations in the blood-brain barrier in these animals are illustrated in Fig. 1. A marked cerebrospinal fluid pressure elevation occurred although there was drainage of a total of from 4 to 6 cc. from each animal over a 4-hour period. Red blood cells were found in varying quantities depending probably on the degree of trauma produced by the needle insertions and subsequent movement. A minimal increase in polymorphonuclear cells was seen in all instances. More impressive were the more numerous large epithelial cells with round densely basophilic nuclei which were found in the cerebrospinal fluid of each animal (Fig. 2). Supravital preparations initially revealed centrally located nuclei but in subsequent smears nuclei lying peripherally were seen. At around 48 hours loss of nuclei of some cells was noted giving to the cell remnant with its open end a basket-like

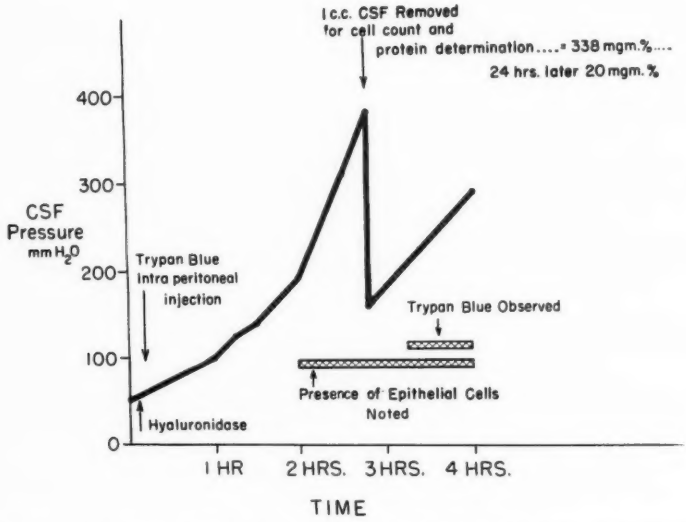

FIG. 1. Representative cerebrospinal fluid changes in cat #4 following cisternal instillation of 9000 units of hyaluronidase.

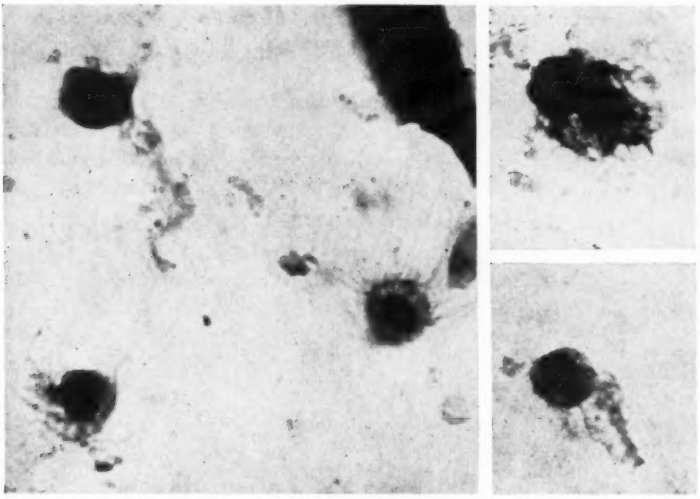

FIG. 2. Photomicrographs (×1080) of epithelial cells seen in smears of cerebrospinal fluid 3 to 4 hours following instillation of hyaluronidase in the cisterna magna of cats. In several cells cytoplasm appears to have broken through the cell membrane.

appearance. Nuclei devoid of cytoplasm resembling those in the epithelial cells were occasionally observed. Sheets or plaques of these cells were often seen. The epithelial cells appeared first at about the end of the second hour of the experiment. They increased in number by the end of 24 hours and thereafter progressively diminished. At 72 hours none could be found.

A breakdown of the blood-brain barrier was evidenced by the appearance of trypan blue in the cerebrospinal fluid at the end of 3 hours. Protein determinations on cerebrospinal fluid samples gave values in the range of 300 mg. per cent at the end of 2 hours but had returned to a normal range within 24 hours (15–25 mg. per cent). *In vitro* addition of 9000 units of hyaluronidase to 1 cc. of cat's cerebrospinal fluid as a control gave a protein determination of 205 mg. per cent. A prolongation of the usual response to pentobarbital anesthesia for a few hours was observed.

Neurological effects occurred which resembled vestibular disturbance and "cerebellar" seizures. These had become manifest at the end of 24 hours and were most pronounced in the monkey. A tendency for right-sided falling, turning movements, and rigidity of the right extremity was noted. In 1 monkey allowed to survive for 6 months these neurological abnormalities had disappeared within 1 month. The cats showed less severe effects and in 2 allowed to survive for 10 and 12 days little if any disability remained. There were no deaths attributed to the central nervous system changes.

At autopsy gross examination revealed no evidence of inflammatory or hemorrhagic reactions. In several instances there appeared to be a marked

reduction of cerebrospinal fluid present in the cisterna magna. This had been noted previously in the same animals when no fluid could be obtained from this region on successive needle punctures.

In both cats and monkeys denuding of the choroid epithelium occurred with the greatest effects found in the 4th and 3rd ventricles. The most marked loss of epithelium appeared in animals sacrificed at the end of 48 hours (Fig. 3). Partial loss of epithelium was in evidence at the end of the

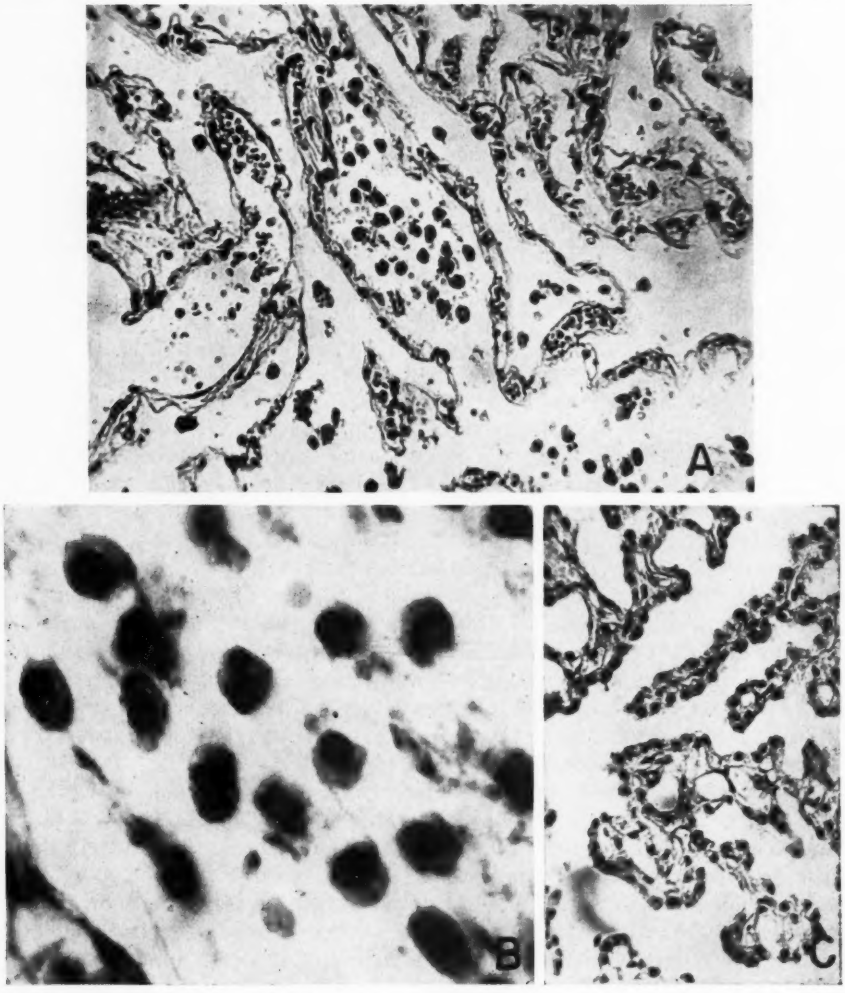

FIG. 3. (A) Denuded choroid epithelium in a monkey sacrificed 36 hours following instillation of hyaluronidase (×570). (B) Higher magnification of same (×1080). (C) Choroid plexus of normal monkey (×570).

5th day. No areas of epithelial loss were seen in those animals sacrificed at the 7th, 10th and 12th days. Some destruction of the ependyma lining the various ventricles aside from the choroid plexus, edema of the cerebellar cortex, especially about the Purkinje cells (Fig. 4), and congestion of some capillaries were also observed in the animals killed in the first 2 days. There was essentially no inflammatory reaction. No changes in the neuronal or glial elements were observed with the methods used.

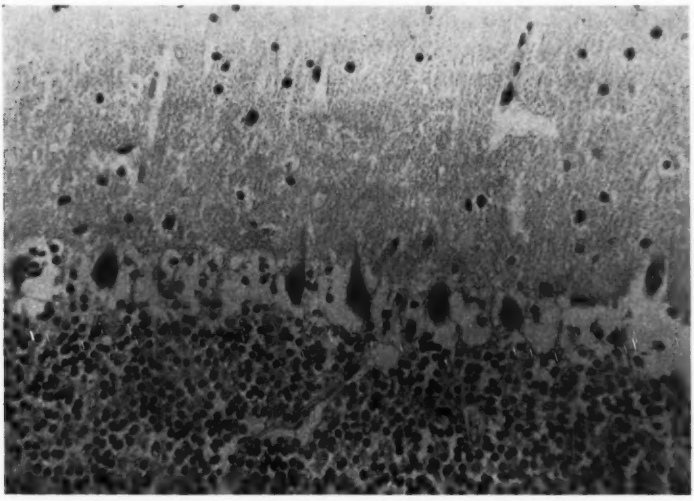

FIG. 4. Cerebellum of cat demonstrating edema about Purkinje cells noted at the end of 48 hours (×570).

The animals in Group III receiving daily cisternal instillations of 1500 units of hyaluronidase for successive periods of 4 and 8 days developed a mild cerebrospinal fluid pleocytosis with daily cell counts ranging from 50 to 300/c.mm. These were predominantly polymorphonuclear leucocytes. In no instances were neurological abnormalities observed. At the end of the experimental period gross and microscopic findings of the brain were within normal limits. No evidence of change in the permeability of the blood-brain barrier was observed in the 2 animals with intraperitoneal trypan blue.

DISCUSSION

Cats and monkeys showed definite concentration tolerance of commercially supplied hyaluronidase injected into the subarachnoid space. The pathological changes were limited primarily to structures immediately in contact with the cerebrospinal fluid containing the dissolved enzyme. The occurrence of neurological changes predominantly on the right side, which

in all instances was the dependent region, is of interest. It suggests that effects of the protein substance were concentrated by gravity.

Despite demonstration that the fluid spreading reaction in subcutaneous areas is unaltered by contact with spinal fluid up to 3 hours and presumably also in the meninges, it is difficult to attribute clinical and pathological changes to specific enzymatic actions directly on the neurons. High osmotic concentrations and foreign protein substances might be able to create local capillary reactions which would produce similar changes. The alteration of the blood-brain barrier as shown by early appearance of trypan blue may be an indication of change in capillary permeability or it could be in part attributed to the change in the barrier by loss of epithelium of the choroid plexus. Spatz[4] in study of the blood-brain barrier demonstrated in dogs that trypan blue appeared in the cerebrospinal fluid in minute amounts only after repeated daily intraperitoneal injections or following intravenous instillation of 20 cc. quantities of a saturated solution of the vital dye. In our experiments the trypan blue used was much less than the above and it appeared in the cerebrospinal fluid in rather profuse amounts within 3 hours following intraperitoneal administration.

Epithelial loss from the choroid plexus began within 2 hours following the instillation of the maximum concentration of the enzyme and apparently reached its peak at around 48 hours. By the 5th day minimal epithelial denuding was still evident and at the end of 7 days no pathology was observed. Regeneration had apparently been accomplished but no direct evidence as to the method was obtained. No mitotic activity was seen. More studies at shorter intervals during the critical period for cytological study of the choroid plexus are planned.

The identification of epithelial cells in the cerebrospinal fluid has not been reported previously. The presence of such cells in this study indicates the possibility of similar changes occurring in various disorders of the central nervous system. Without careful study of them in stained smears under proper magnification such cells could easily be mistaken for leucocytes.

Two hours following instillation of hyaluronidase the cerebrospinal fluid protein ranged from 296 to 338 mg. per cent. These figures are significantly greater than the protein (205 mg. per cent) found in the control sample made of 1 cc. of cerebrospinal fluid to which 9000 units of the enzyme were added. During the initial stages of each experiment, if the rise of intracranial pressure is allowed as evidence, there is probably an increased amount of cerebrospinal fluid which would serve to dilute the added protein. And so the protein in the cerebrospinal fluid of the experimental animal is relatively high. The recorded differences must therefore represent an addition of protein from a source within the animal. Speculation as to the source implicates the choroid plexus since there is simultaneous evidence of cellular damage and loss. It is possible that the increased protein could be derived from the denuded cells, themselves, but at present this has not been determined. A more probable explanation is that the additional protein came from the blood

serum through the altered blood-brain barrier. Within 24 hours after the hyaluronidase injection the protein in the cerebrospinal fluid had dropped and remained at relatively normal levels (15–25 mg. per cent). This rapid return to normal remains unexplained.

Recent reports of the effective suppression by hyaluronidase of torula organisms studied *in vitro*[2] and demonstrations of such in the bacteriological laboratory here[3] are of interest. At concentrations of 8 to 10 turbidity reducing units the inhibition of torula growth was noted. As demonstrated effectively in this study concentrations of 1500 turbidity reducing units/cc. were tolerated without undue reactions when inserted into the cisterna magna of experimental animals. It is suggested therefore that clinical trial at high concentrations should be feasible.

SUMMARY

Responses of the central nervous system to various concentrations of hyaluronidase introduced via the cisterna magna have been studied in cats and monkeys. Concentrations of 6000–9000 turbidity reducing units produced temporary clinical changes related to the animals' position during the initial study and perhaps to the local cerebellar alterations. Occurrence of choroid epithelial cells was noted in the cerebrospinal fluid. Microscopic studies revealed denuding of the choroid plexus and partial loss of ependyma. Tolerance of daily injections of 1500 turbidity reducing units without significant microscopic pathological or clinical changes was noted. It has been suggested that high concentrations of hyaluronidase would be tolerated clinically without undue side effects. It is suggested that the presence of previously unrecognized epithelial cells in the cerebrospinal fluid may occur in clinical disorders.

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LONG-TERM FOLLOW-UP OF 106 CASES OF ASTROCYTOMA, 1928–1939*

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(Received for publication February 14, 1956)

IN 1926 Bailey and Cushing[1] divided the astrocytomas into fibrous and protoplasmic subgroups which may occur in the cerebrum or in the cerebellum. In 1935 it was suggested by Elvidge, Penfield and Cone[2] that the astrocytomas could be practically divided into three subgroups. This classification was based upon the clinical and histological study of some 55 cases of astrocytoma. At the time it was felt that these tumours presented a rather characteristic histological picture and manner of growth and fell naturally into their respective groups from a clinical and statistical point of view.

The present survey is based upon a total of 112 cases of astrocytoma occurring in the period November 1928–December 1939 (11 years) with a long-term follow-up in 90 per cent of the cases until June 1953. Of these 112 cases, 6 have been finally omitted in the subgrouping–2 tumours considered as glioblastoma multiforme, 1 an intramedullary cyst without sections available and 3 tumours considered as malignant astrocytomas unclassified.

Of the remaining 106 cases, 53 fell into the piloid subgroup, 29 into the diffusum, and 24 into the gemistocytic.

ASTROCYTOMA DIFFUSUM

29 cases (25.8 per cent)

Astrocytoma diffusum has been the most difficult astrocytoma to classify, and the last to be recognized as a definite subgroup of practical value in our series. The type cell is a small, stellate astrocyte. In most instances it is difficult to find any formation of neuroglial fibrils and some would undoubtedly prefer to call this therefore a protoplasmic astrocytoma. The tumour is very invasive, penetrating widely the gray and white matter in all directions. While involving the gray matter, the cells do not tend to form fibres, but when they invade the white matter they may appear as small fibrous astrocytes. One cannot therefore be satisfied with merely calling this a protoplasmic astrocytoma. The protoplasmic astrocytoma described by Bailey and Cushing occurred both in the cerebral and cerebellar hemispheres, whereas the astrocytoma diffusum has been found by us only in the cerebral hemispheres.

* A review of 176 cases of astrocytoma for the ten-year period from 1940–1949 has been made by L. F. Levy and A. R. Elvidge, *J. Neurosurg.* (in press).

The tumour grows in a rather characteristic fashion, invading brain tissue in a most insidious manner, and with a minimum amount of change in gross appearance. It is rather difficult, therefore, to recognize its limits at postmortem examination, and even its presence at operation. Horizontal section through the brain will show generally an enlarged hemisphere, and the line of demarcation between the tumour and normal brain will not be easily evident. Surgically exposed, the cortical surface may appear somewhat whitish or light yellow in colour, and there may or may not be widening of convolutions. The neoplastic cells spread beneath the pia mater forming more cellular nodes of growth. It enters the white matter, where it spreads widely and deeply in all directions, turning up at one point and then another, and may invade the corpus callosum.

In the gray matter, the cells wander amongst the nerve cells without causing them to show signs of degeneration. For this reason the tumour has sometimes been mistaken for a ganglioneuroma. (In 2 cases of our series the possibility of ganglioneuroma was considered; the first tumour was finally classified as a piloid astrocytoma with inclusion of neurones and the other as an astrocytoma diffusum with typical areas of increased satellitosis.) It is characteristic for the cortical nerve cells to be surrounded by a fair number of tumour satellites. In fact, satellitosis is a distinguishing feature in this tumour. Mitotic figures are sometimes fairly frequent, and one or more were found in 34.4 per cent of our cases. In some cases more embryonic cell types, unipolar and bipolar cells were found.

Areas of degeneration and cystic formation do not as a rule occur, and beyond the finding of microscopic cysts in very few tumours, none have shown gross cyst formation. There are no particular vascular changes that are characteristic. It is difficult to place this tumour in any category proposed by Svien *et al.*[6]

The average age of the patient at the time of admission to the hospital for diagnosis and therapy was 33.7 years. The ages of all patients at the time of their first admission for treatment are grouped by decades in Table 1. Thirteen of the 29 patients (44.8 per cent) were in the 4th decade of life.

Considering sex distribution in the 29 cases of astrocytoma diffusum 16 (55.1 per cent) occurred in males and 13 (48.8 per cent) in females (Table 2).

Of the 29 tumours, 27 were located in the cerebral hemispheres, and 2 in the 3rd ventricle involving basal ganglia. No instance of astrocytoma diffusum of the cerebellum has been found in this series. An approximate summary of their localization is shown in Table 3.

The average pre-operative duration of symptoms was 27.6 months. This figure is similar for the piloid and gemistocytic groups (Table 4).

Epilepsy occurred in 21 of the 29 cases, i.e. 72 per cent. It was the first symptom to appear in 18 instances (62 per cent). Also in 18 cases (62 per cent) the attacks were described as focal and in 3 (10.3 per cent) as generalized.

TABLE 1

Astrocytoma diffusum—age incidence in 29 cases

Years	0–10	11–20	21–30	31–40	41–50	51–60
No. of cases	3	1	6	13	4	2

TABLE 2

Sex distribution in 106 cases of astrocytoma

Subgroup	Total	Male	Female
Piloid	53	35 (66%)	18 (34%)
Gemistocytic	24	15 (62.5%)	9 (37.5%)
Diffusum	29	16 (55.1%)	13 (48.8%)

TABLE 3

Astrocytoma diffusum—localization

Left hemisphere (10)		Right hemisphere (17)	
Frontal	2	Frontal	4
Parietal	1	Parietal	5
Temporal	3	Temporal	5
Temporofrontal	2	Frontotemporal	1
Temporoparietal	1	Frontotemporoparietal	1
Basal ganglion (thalamus)	1	Occipitotemporal	1
	3rd ventricle—2		

TABLE 4

*Average duration of symptoms previous to operation**

Subgroup and Location	Cases	Months
Diffusum (cerebrum)	29	27.6
Gemistocytic (cerebrum)	24	29.8
Piloid (encephalon)	52	24
Not including 3rd ventricle and mesencephalon (cerebrum)	24	29.6
Cerebellum	21	20.5

* One case of piloid astrocytoma of the spinal cord has been omitted from this table.

TABLE 5

Astrocytoma diffusum (19 cases)
Postoperative survival of each patient

Years $\frac{1}{2}$, $\frac{1}{2}$, $\frac{1}{2}$, $\frac{1}{2}$, 1, 1, 1, $2\frac{1}{2}$, 3, 3, 5, 8, 9, 10, 10, 13, 13, 13,* $13\frac{1}{2}$

* Alive and well.

Among the 29 cases, there were 7 operative deaths (24.3 per cent) and 3 cases in which the postoperative course is unknown. Nineteen cases of astrocytoma diffusum were available for follow-up (Table 5). Seven (36.8 per cent) of these patients died within the first year after operation, 3 (15.3 per cent) died within the 3rd postoperative year, 1 (5.2 per cent) died 5 years after operation and 8 (42.1 per cent) survived for more than 8 years, bringing the average postoperative survival for the whole group of 19 cases to 5 years and 4 months. The average pre-operative duration of symptoms (Table 4) was $2\frac{1}{3}$ years—making an average total evolution of the disease of 7 years and 8 months, almost 8 years.

As far as treatment is concerned, in most of the cases it is not possible to perform a complete surgical removal of the tumour, but partial removal and decompression followed by X-ray therapy seem to give satisfactory results; i.e. one patient (Case 39) survived for 13 years after partial removal and decompression even though having headaches, epilepsy and one arm paralyzed. Two other patients (Cases 91 and 106) showed signs of recurrence 7 years after operation—Case 91 had partial removal, decompression and X-ray therapy, and died 12 years and 10 months after operation; and Case 106, who had partial removal and re-operation 9 years and 5 months later, died 6 months after re-operation. Case 56 showed signs of recurrence 9 years after what was considered to be a complete removal of the tumour without postoperative X-ray therapy. He was re-operated upon and a full course of deep X-ray therapy was given. He died $4\frac{1}{2}$ years later, $13\frac{1}{2}$ years after the first operation. Case 88 should be considered, we believe, as an example of a 9 years' total evolution of an astrocytoma diffusum without any kind of therapy; this patient started to have generalized seizures and occasional headaches at the age of 30 becoming gradually worse until the time of death 9 years later during one of the attacks. At autopsy an astrocytoma diffusum was found involving the right frontoparietotemporal lobes. Finally, one of our patients (Case 87) is still living almost 13 years after partial removal and decompression followed by X-ray therapy; this patient is having occasional epileptic attacks, and has a right hemiparesis and some speech difficulty.

A summary of the cases in which the postoperative survival was more than 8 years is given in Table 6.

GEMISTOCYTIC ASTROCYTOMA

24 cases (21.4 per cent)

The type cell of this group is the Nissl plump cell or gemistocytic astrocyte forming, as a rule, a few fibrils.

The term *gemästete*, which means "fed or fattened up," was used by Nissl when the cell was confused with the compound granular corpuscle. The word gemistocytic is derived from the Greek adjective *gemistos*, meaning "filled up."

TABLE 6

Astrocytoma diffusum

Therapy and follow-up in 7 cases of more than 8 years' postoperative survival

Case No.	Therapy	Postoperative Survival	Condition of Patient
63	Complete removal; X-ray therapy	8 yrs. Dead	In good condition few years. Died of cerebral thrombosis; recurrence of tumour
30	Complete removal	10 yrs. Dead	Left hemiparesis
106	Partial removal and re-operation	10 yrs. Dead	Mild left hemiparesis after operation but free of attacks for 7 yrs. Recurrence of focal seizures with increase of hemiparesis
39	Partial removal and decompression	13 yrs. Dead	Paralysis of left arm, headaches and epilepsy
87	Partial removal and decompression; X-ray therapy	13 yrs. Alive	Occasional epileptic attacks, right hemiparesis and speech difficulty
91	Partial removal and decompression; X-ray therapy	13 yrs. Dead	Epilepsy. Signs of recurrence 7 yrs. after operation
56	Complete removal and re-operation 9 yrs. later. X-ray therapy after 2nd operation	13½ yrs. Dead	Left hemiplegia, epilepsy. Recurrence 9 yrs. after operation

It might be objected at once that this is a reacting cell and therefore should not be considered as a neoplastic cell. But tumours were found that were almost entirely composed of these cells, which seemed to justify the classification. It seems likely that there is a toxic or a vascular reaction affecting the tumour cells as may occur in other pathological states. Tumour cells have been observed passing through the pia mater and coming to lie in the subarachnoid space adjacently, still being recognizable as Nissl plump cells, but having lost their processes. Most tumours are of mixed cell type and they are then classified according to the prevailing type of cell and placed in this subgroup only if the histological picture is strongly suggestive.

This tumour invades both gray and white matter and the gray cortex can be seen to be much thickened (widened). One or more mitotic figures were found in 29 per cent of cases.

On cross section of the brain, the limits of the tumour may be fairly well visualized and at operation the surface convolutions may be seen to be much widened and flattened and the cortical surface may show a yellowish and sometimes a pinkish colour. In this series this tumour has been found only in the cerebral hemisphere. Tumours of this type were described by Lotmar[3] (1918) as Amöboidzellengliom and as astrocytome giganto-cellulaire by Roussy and Oberling[5] (1931) and again as plump cell astrocytoma by Penfield[4] (1932). In 1935, Elvidge, Penfield and Cone[2] suggested the term gemistocytic astrocytoma be considered as a definite subgroup of astrocytoma, when a growth of seemingly pure culture was found. It is again difficult to place this tumour in the classification of Svien, *et al.*[6] (1949). It would

probably correspond to Group III but is certainly not synonymous with glioblastoma multiforme.

Another point of differentiation in this subgroup is the interesting fact that large cystic formation is uncommon, though gross medium-sized cysts within the tumour occur in a certain number of cases. Of the 24 gemistocytic astrocytomas 7 (29 per cent) were cystic—4 cases of large intraneoplastic cysts, and 3 of small ones.

There were 18 cases available for follow-up. Fourteen patients had noncystic and 4 had cystic tumours (2 with large cysts and 2 with small ones). In the group of 14 noncystic cases, the average postoperative survival was 3 years and 9 months. For the 4 cystic cases the average postoperative survival was 2 years and 9 months. These values suggest that cyst formation in the gemistocytic group does not necessarily mean a slower rate of growth as seems to be the case in the piloid variety of astrocytomas.

In the present series all of the gemistocytic astrocytomas occurred in the cerebrum (1 in the III ventricle and the remainder distributed in the cerebral hemispheres). Their gross distribution is indicated in Table 7.

The average age of the patients was 38.2 years, and excluding the case of III ventricle tumor (patient aged 10) the average age for the remaining 23 cases was 39.4 years. If we compare this figure with those of the other two types of astrocytoma, it seems that the gemistocytic type occurs in an older group (Table 8).

The age of each patient at the time of admission is set forth by decades in Table 9.

TABLE 7

Gemistocytic astrocytoma—localization

Left hemisphere (14)		Right hemisphere (9)	
Frontal	4	Frontal	4
Parietal	3	Temporal	3
Temporal	5	Frontoparietal	1
Temporoparietal	1	Basal ganglion	1
Parieto-occipital	1		
	3rd ventricle—1		

TABLE 8

Astrocytomas—average age of patients

Subgroup	Number of Cases	Average Age (years)
Piloid	53	26*
Diffusum	29	33.7
Gemistocytic	24	38.2

* See also Table 14.

TABLE 9

Gemistocytic astrocytoma—age incidence in 24 cases

Years	0–10	11–20	21–30	31–40	41–50	51–60
No. of cases	1	0	2	11	9	1

In the gemistocytic group the incidence of positive history of cancer in the family is 4 times higher than in the other two groups of astrocytomas (Table 10).

The average pre-operative duration of symptoms was 29.8 months (Table 4).

Epilepsy occurred in 14 of the 24 cases (58.1 per cent). In 11 cases (45.8 per cent) it was described as focal and in 3 cases (12.5 per cent) as unlocalized epilepsy. Epilepsy was the first symptom of the disease in 11 of 24 cases (45.8 per cent).

TABLE 10

Astrocytomas—Positive history of cancer in the family
106 cases—No data in 13

Subgroup	No. of cases	Positive history	Per Cent
Piloid	47	4	8.5
Diffusum	25	2	8.0
Gemistocytic	21	7	33.3

Finally on looking at the follow-up values in the group of 24 cases of gemistocytic astrocytoma, there were 6 (25 per cent) operative deaths (5 within the first postoperative week, and 1 three months after operation) and 18 cases available for follow-up. Of these 18 patients, 5 (27.7 per cent) died within the first postoperative year, 5 (27.7 per cent) survived less than 3 years, and 8 (44.4 per cent) survived from 4 to 10 years after operation (Table 11). The average postoperative survival for these 18 cases was 3 years and 8 months. The average pre-operative duration of symptoms was 28 months and the average total evolution or duration of the disease was 6 years.

Most of the patients continued having epilepsy postoperatively. One (Case 27) remained free of attacks for $5\frac{1}{2}$ years after operation, presenting

TABLE 11

Gemistocytic astrocytoma (18 cases)
Postoperative survival of each patient

Months	4, 8, 8, 8, 10
Years	$1\frac{1}{2}$, $1\frac{1}{2}$, 2, 2, $2\frac{1}{2}$, 4, $4\frac{1}{2}$, $5\frac{1}{2}$, $5\frac{1}{2}$, 7, $7\frac{1}{2}$, $7\frac{1}{2}$, 10

signs of recurrence of the tumour 6 months later and finally dying 7 years after operation. At autopsy the tumour was classified as glioblastoma multiforme, though with fairly complete surgical removal $6\frac{1}{2}$ years before, sections had shown typical gemistocytic astrocytoma in pure culture. This is the only direct evidence that we have noted of a glioma apparently changing its pace. It may have been a glioblastoma multiforme from the beginning.

The patients with the longest average postoperative survival after complete single removal of the tumour are those with the shortest average preoperative symptomatology (Table 12). These figures suggest that a longer

TABLE 12

Gemistocytic astrocytoma—complete surgical removal
Postoperative survival and pre-operative duration of symptoms

No. of Cases of Complete Single Removal	Average Postoperative Survival	Average Pre-operative Duration of Symptoms
1st group (4 cases)	7 years	1.5 years
2nd group (6 cases)	1.5 years	3 years

postoperative survival may be expected in this group of astroyctomas with earlier surgical treatment.

PILOID ASTROCYTOMA

53 cases (47.3 per cent)

The third group is what is termed the piloid astrocytoma. The cell type is a piloid astrocyte of variable size forming fibrillae. In a former unpublished review occasional mitotic figures were discovered in just under 21 per cent of cerebral and cerebellar cases. In contradistinction to the subgroups described above these commonly arise both in the cerebrum and in the cerebellum and also in the spinal cord. These tumours as a whole occur at a younger average age (26 years) than in the case of the two preceding subgroups (Table 8). The age incidence is more evenly distributed over the first six decades of life; in our series the largest number of cases (16 of 53, or 30 per cent) fell into the second decade of life at the time of admission to the hospital (Table 13).

It was the experience of Bailey and Cushing[1] that cerebellar astrocytomas, at least the "protoplasmic" type, occurred at a younger age than did the cerebral. This is confirmed for this tumour subgroup. The average age of 24 patients with piloid astrocytoma of the cerebral hemisphere was 31.5 years, while the average age of 21 with cerebellar tumours was 20.8 years. It is interesting that the midline cerebellar cases exhibit an average age of only 12 years in the present series, in contrast to the cerebellar hemi-

TABLE 13

Piloid astrocytoma—age incidence in 53 cases

Years	0–10	11–20	21–30	31–40	41–50	51–60
No. of cases	9	16	6	8	11	3

spheral cases which exhibit an average age of 34.8 years (Table 14). This observation has not been substantiated in another later series of cases.

The localization of the piloid astrocytomas is presented in Table 15.

The average duration of symptoms previous to operation was 24 months in 52 cases of piloid astrocytoma (1 case of spinal cord tumour with preoperative symptoms for 1 month has been omitted). For the 24 cerebral hemispheral cases the average duration of symptoms previous to operation was 29.6 months and for the 21 cerebellar cases 20.5 months (Table 4).

It is characteristic of this group of tumours to form large cysts about a mural nodule. This is specially true when they arise in the cerebellum. Of the total 52 piloid astrocytomas cyst formation was present in 26 cases (50 per cent). The distribution of these tumours is given in Table 16.

TABLE 14

Piloid astrocytoma—age distribution and location in 53 cases

Location	No. of Cases	Average Age (years)
Cerebral hemispheres	24	31.5
Cerebellar	21	20.8
Cerebellar midline	13	12.2
Cerebellar hemisphere	8	34.8
Brain stem, III ventricle and spinal cord	8	27.0

TABLE 15

Piloid astrocytoma—localization

Cerebral—24			
Left hemisphere (12)		Right hemisphere (12)	
Frontal	3	Frontal	1
Temporal	4	Parietal	2
Parietal	1	Temporal	4
Occipital	1	Parietotemporal	2
Frontoparietal	2	Parietotemporo-occipital	1
Basal ganglion	1	Basal ganglion	2
III ventricle—4			
Midbrain and aqueduct of sylvius—3			
Cerebellar—21			
Left hemisphere	5	Right hemisphere	3
Midline	13		
Spinal cord—1			

TABLE 16

Piloid astrocytoma—cyst formation

Location	No. of Cases	Cyst Formation	Per Cent
Cerebellar	21	16	76.0
Cerebral hemisphere	24	9	37.5
III ventricle and midbrain	7	1	14.2

As Penfield described, the fluid of such cysts forms as a transudate outside the tumour, so that the tumour comes to lie as a mural nodule. The remaining portion of the wall of the cyst is then composed of possibly non-neoplastic astrocytes from the substance of the brain. Cysts may also occur within the tumour tissue itself. This is more typical of the gemistocytic astrocytoma and other types of glioma. The mechanism of formation is not clear. It is possible that the cyst fluid is formed through the breakdown of protoplasmic processes. Microscopically, one may follow the cytoplasm of the astrocyte to a point where it seems to melt into the fluid material of the cyst cavity.

Epilepsy was present in 18 (75 per cent) of the 24 cases of piloid astrocytoma of the cerebral hemisphere. It was described as focal in 13 (54 per cent) and as general in 5 (20.8 per cent). Epilepsy was the first symptom of the disease to occur in 13 (54 per cent) of 24 cases. This figure was higher in the astrocytoma diffusum group and lower in the gemistocytic group, as can be seen in Table 17.

Follow-up of the 53 cases of piloid astrocytomas operated upon showed there were 12 operative deaths (22.4 per cent), 2 cases of unknown follow-up and 39 cases available for follow-up. Of these 39 patients, 12 (30.7 per cent) survived less than 2 years; 8 (20.5 per cent) died within the second and fifth postoperative year inclusive, and 19 (48.7 per cent) survived more than 5 years after operation up to $23\frac{1}{2}$ years, the average postoperative survival to date being 8.5 years (Table 18).

The average postoperative survival in the 20 cerebral hemispheral cases was 7 years. In the 14 cerebellar cases, the average postoperative survival was 13 years (10 midline cases, average 12 years; 4 cerebellar hemispheral cases, average 14 years). In the other 5 cases, in which the tumours were

TABLE 17

Epilepsy in cases of astrocytoma of cerebral hemispheres

Subgroup	No. of Cases	Incidence of Epilepsy Per Cent	Focal Seizures Per Cent	General Seizures Per Cent	Seizure as First Symptom Per Cent
Diffuse	21	72.0	62.0	10.3	62.0
Gemistocytic	24	58.1	45.8	12.5	45.8
Piloid	24	75.0	54.0	20.8	54.0

TABLE 18

Piloid astrocytoma (39 cases)
Postoperative survival of each patient (years)

Cerebral hemispheres (20 cases)
$\frac{1}{2}$, $\frac{1}{2}$, 1, $1\frac{1}{2}$, $1\frac{1}{2}$, $1\frac{1}{2}$, 2, 2, 3, $3\frac{1}{2}$, $3\frac{1}{2}$, $4\frac{1}{2}$, 5, 8, 12, 13,* 15,* 18,* 23, $23\frac{1}{2}$*

Cerebellar (14 cases)
$\frac{1}{2}$, $1\frac{1}{2}$, 6, $6\frac{1}{2}$, 10, 12, 13,* $14\frac{1}{2}$,* $14\frac{1}{2}$,* 17,* 18,* 21,* $21\frac{1}{2}$,* 23*

Basal ganglia (1 case)
$1\frac{1}{2}$

III ventricle (1 case)
4

Aqueduct of Sylvius (2 cases)
$\frac{1}{2}$, 1

Spinal cord (1 case)
$\frac{1}{2}$

* Alive at the present time.

located in the III ventricle, basal ganglia, midbrain, and spinal cord, the average postoperative survival was only 1 year and 4 months.

In the group of 20 cerebral hemispheral tumours, 8 were cystic (40 per cent). In the cerebellar group of 14 cases, there were 9 cystic tumours (66.6 per cent). In the other 5 tumours distributed in the III ventricle, basal ganglia, midbrain and spinal cord, cyst formation was not present.

In the 8 cases of cystic tumours of the cerebral hemispheres the average postoperative survival was 11.9 years. In the 12 cases of noncystic tumours the average postoperative survival was 3.8 years. In the cerebellar group the average postoperative survival in the 9 cases of cystic tumours was 16.9 years and in the 5 cases of noncystic tumours it was 6.5 years (Table 19).

Of the 19 patients who survived more than 5 years, 12 are still alive. The remaining 7 patients had the following course:

Case 1 (cystic piloid astrocytoma of right parietal lobe). Partial removal of tumour; re-operation $3\frac{1}{2}$ years later for refilling of the cyst; again re-operation $2\frac{1}{2}$ years later, this time with re-evacuation and communication of the cyst to the lateral ventricle. Patient died 23 years after the first operation, having focal epilepsy and a left hemiparesis.

Case 18 (cystic, cerebellar). Partial removal of tumour. Patient died 6 years after operation, able to walk and blind.

Case 29 (cystic, cerebellar). Complete removal; re-operation 4 years later; re-operation 4 months later; re-operation 5 years later. Condition: signs of recurrence 3 years and 8 months after first operation. No improvement after second operation. Relatively well after third operation with some ataxia and speech difficulty for the

following 4½ years and finally gradually downhill for 3 years and 8 months after the last operation. Died.

Case 36 (cerebral hemisphere, noncystic). Complete removal; re-operation 9 years and 8 months later. Free of attacks for 6 months; severe epilepsy for the following 9 years. Died 3 years after re-operation.

Case 105 (cerebral hemisphere, noncystic). Partial removal plus X-ray therapy. Epilepsy gradually diminishing and finally free of attacks for 3 years. Died 7 years and 4 months after operation.

Cases 5 and 11 (cerebellar, noncystic). Both patients had complete removal of the tumour and died 10 and 6½ years respectively after operation, the postoperative condition of the patients being unknown.

Twelve patients are living at the present time (4 cerebral and 8 cerebellar cases). Cyst formation was present in 11 cases. The other patient (Case 82, cerebellar midline, noncystic) is now, 14½ years after complete removal of the tumour, in perfect physical condition.

Complete surgical removal of the tumour as the only therapeutic procedure was performed in 10 of these 12 cases, except one in which X-ray therapy was also given for 10 days following operation.

Of the other 2 cases, in one (Case 13) re-operation was necessary 16½ years after complete removal of midline cerebellar tumour for evacuation of a cyst. There was no tumour recurrence. The patient had been in good health for 15 years, then there developed major and minor epileptic attacks, headache, and difficulty with walking. The patient is now, 7 years after evacuation of the cyst, in perfect physical condition. The other patient (Case 108) had first a suboccipital decompression and 5½ years later a complete removal of the tumour (cerebellar, midline cystic). The patient is now, 13 years after the complete removal of the tumour, in perfect physical condition.

In the group of 12 patients alive at the present time, 8 (2 cerebral, 6

TABLE 19

Piloid astrocytoma (39 cases)
Location, cyst formation and average postoperative survival

Location of Tumours and Incidence of Cyst Formation	Average Postoperative Survival (years)
Brain hemispheres (20 cases)	
Cystic—8 cases (40%)	11.9
Noncystic—12 cases	3.8
Cerebellar (14 cases)	
Cystic—9 cases (66.6%)	16.9
Noncystic—5 cases	6.5
III ventricle, basal ganglia, midbrain and spinal cord (5 cases)	
Noncystic—5 cases	1.0

cerebellar) have an A.S.E.* rating of *4.4.4*, that is, they are completely well anatomically, symptomatically and economically. The condition of the other 4 patients (2 cerebral, 2 cerebellar) is as follows:

Case 44 (right temporal, cystic). Complete removal. Eighteen years after operation, patient is well but blind as she was before operation.

Case 52 (cerebellar, cystic). Complete removal. Eighteen years after operation, patient is well but unable to work because of marked diminution of visual acuity, nystagmus and slight cerebellar symptoms (all these neurological disabilities were present before operation).

Case 81 (cerebellar, cystic). Complete removal. Fourteen and one-half years after operation, A.S.E. rating is 4.3.4 (sequelae of slight cerebellar dysfunction).

Case 110 (right temporal, cystic). Complete removal. Thirteen years after operation, there is paralysis of the left arm, the left side of the body is less developed than the right, and the patient is mentally retarded. (The patient had a left hemiplegia before the operation.)

The average age of the 12 living patients at the time of admission was 18.7 years. The average duration of symptoms previous to operation was $3\frac{1}{2}$ years, and the average postoperative survival to date is *18 years*.

APPENDIX

The following 6 cases were omitted from the preceding series because of malignancy. *They are appended here only to show that longevity is still possible.*

Case 20. Question of piloid astrocytoma, finally classified as glioblastoma multiforme. Left frontal, cystic. Partial removal. Died 18 days after operation of bronchopneumonia.

Case 26. Question of piloid astrocytoma, astroblastoma, finally classified as glioblastoma multiforme. Right temporal, noncystic. Partial removal. Died $1\frac{1}{2}$ months after operation.

Case 83. Malignant type of astrocytoma, astroblastomatous arrangement at times, question of glioblastoma multiforme. Left frontal, cystic. Complete removal. Died at home approximately 10 years after operation. Postoperative condition unknown.

Case 92. Malignant type of astrocytoma. Right frontal, cystic. Complete removal. X-ray therapy (4000 r). Re-operation 4 years and 9 months later. Died 6 months after re-operation. Patient was fairly well for 4 years and 5 months after the first operation. At autopsy question of classifying the tumour as a "low-grade" glioblastoma multiforme.

Case 104. Malignant type of astrocytoma. Right parietal, cystic. Partial removal. Postoperative X-ray therapy (7950 r). Died 6 months after operation of a heart attack.

Case 109. Intramedullary tumour at level of C6. Suspected astrocytoma. Explor-

* A.S.E. = anatomically, symptomatically, economically. Grading is from 0–4, 4 being 100 per cent.

atory laminectomy and biopsy. Insufficient material for pathological diagnosis. No paraffin sections. Patient died 4 months after operation.

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HYPOTHERMIA AND CEREBRAL VASCULAR LESIONS

I. EXPERIMENTAL INTERRUPTION OF THE MIDDLE CEREBRAL ARTERY DURING HYPOTHERMIA*

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INTRACRANIAL surgery in the treatment of cerebral vascular anomalies has been sharply limited by the numerous hazards attendant such procedures. Not only is the task of achieving hemostasis frequently difficult, but it is often made more formidable by the risk of producing a neurological deficit through the interruption of a major vascular channel. A technique that could minimize or obviate this risk would make it possible to perform definitive and curative surgery for many lesions that now are commonly considered inoperable. This communication presents an experimental approach to this problem.

It has been well established that permanent occlusion of the middle cerebral artery in the normothermic dog produces an area of infarction of significant magnitude.[6,8,11,14] This is proportional to the degree and to the rapidity of the occlusion.[9] It was therefore postulated that a marked reduction of cerebral metabolism at the time of occlusion would provide more advantageous conditions for the establishment of collateral circulation, thereby resulting in the modification or prevention of infarction. The following experiments suggest that such conditions may be attained with the use of hypothermia.

METHODS

Thirty-seven mongrel dogs weighing between 10.0 and 22.0 kg. and unselected as to age and sex were used in this investigation.

Twenty-four hours before each experiment, the dogs were given long-acting Benzathine penicillin G, 600,000 units, intramuscularly, and diphenylhydantoin sodium, 0.4 gm., orally. The diphenylhydantoin sodium was administered daily through the 5th postoperative day in order to suppress convulsions.

Anesthesia was achieved with intravenous pentobarbital sodium, 30 mg./kg. Body hair was removed with clippers, and the dogs were intubated with a cuffed No. 38 Fr. endotracheal catheter. The catheter was attached to an automatic posi-

* The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

The pilot study preliminary to this investigation was reported at the Annual Meeting of the Federation of American Societies for Experimental Biology, April 11–15, 1955.[15] The author was then a member of the Department of Neurological Surgery, Columbia University College of Physicians and Surgeons and the Presbyterian Hospital, New York City.

tive-negative pressure closed-system respirator† which delivered 100 per cent oxygen at a rate of 24 respirations per min. The positive pressure was adjusted between 7 and 11 mm. Hg and the negative pressure between 1 and 4 mm. Hg in order to maintain a tidal exchange of 200–400 ml. A thermistor was inserted 200 mm. into the esophagus for the recording of body temperature. The animals were immersed to the shoulders in ice water until the esophageal temperature fell to 25°C. They were then transferred from the ice bath to the operating table. Body temperature decreased an additional 1–3°C. while the animals were being prepared for surgery.

With the dog in the right lateral recumbent position, a left subtemporal craniectomy was performed using aseptic technique. The dura mater was incised and the pyriform lobe was gently retracted to expose the middle cerebral artery. The artery was freed from its meningeal investment for the first few millimeters of its course, great care being exercised not to disrupt any important adjacent vascular structure. The artery was then transected between silver clips at its origin. Arrow No. 1 in Fig. 1 indicates the point of transection. The dura mater was approximated over strips of absorbable gelatin sponge and the incision was closed in layers utilizing stainless steel screening to cover the craniectomy defect. Two variations of this procedure were also utilized. One consisted of a "crotch isolation"; i.e. division of the middle cerebral artery combined with occlusion of the ipsilateral internal carotid, posterior communicating, and anterior cerebral arteries. The second was a segmental resection of the middle cerebral artery from its origin to the first major cortical bifurcation. This included coagulation and section of each central (striatal) branch and the anterior choroidal artery which, in the dog, arises from this segment of the middle cerebral artery. The section of artery removed corresponds to that indicated between arrows No. 1 and 2 in Fig. 1.

At the termination of the operative procedure, each animal was rewarmed in a water bath in which the temperature was maintained 10°C. higher than that of the dog, until a body temperature of 35°C. was reached. Rewarming was then discontinued and the animal was allowed to spontaneously regain the normothermic state. All animals were observed for 18–22 days. They were then reanesthetized and sacrificed by formalin perfusion. The brains were removed and studied grossly and microscopically.

Occlusion of the middle cerebral artery in the normothermic dog produces a triad of clinically detectable manifestations. These are: (1) ipsilateral forced circling movements, (2) a contralateral hemiparesis, and (3) a contralateral temporal homonymous visual field defect. A visual field defect was said to be present when no reaction was obtained in response to the examiner's finger movements or when the animal obviously bumped into objects placed in the suspected field of vision. The animals were examined daily and the presence or absence of any or all of the above signs was recorded. No attempt was made to evaluate the clinical signs during the first 48 hours postoperatively, since it was difficult to differentiate the transient signs caused by operative handling from those resulting from permanent brain damage. The subsequent course was divided into 5 periods, as follows:

† Designed by Dr. D. A. Holaday and constructed by the Metal Model Shop of the Naval Medical Research Institute with parts supplied by the Ohio Chemical & Surgical Equipment Company.

Period 1—3 to 5 postoperative days.
Period 2—6 to 8 postoperative days.
Period 3—9 to 11 postoperative days.
Period 4—12 to 14 postoperative days.
Period 5—15th day to day of sacrifice.

A neurological score was computed for each animal. One point was given for each of the clinical signs, when present, and this was multiplied by the number of postoperative periods during which it persisted. Thus, the maxi-

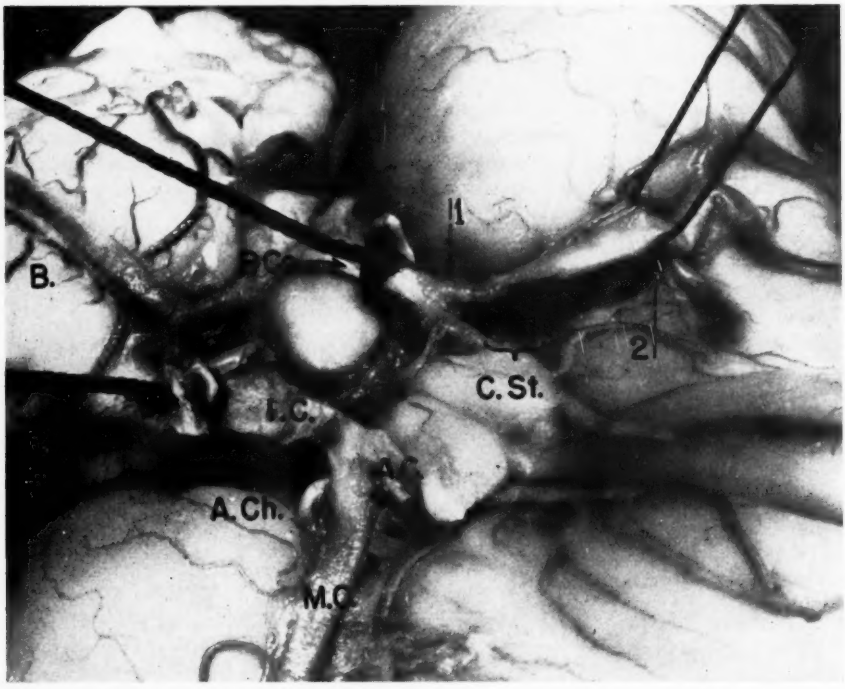

FIG. 1. Basal view of a dog brain demonstrating the vascular relationships about the middle cerebral artery. M.C., middle cerebral artery, A.Ch., anterior choroidal artery, C.St., central (striatal) arteries. A.C., anterior cerebral artery, I.C., internal carotid artery, P.Co., posterior communicating artery, B., basilar artery, Arrow 1, origin of the middle cerebral artery, Arrow 2, first major cortical bifurcation of the middle cerebral artery.

mum score obtainable was 15. In every animal in which the subtemporal exposure was used, including sham-operated controls, a transient ipsilateral oculomotor paresis developed. This disappeared by the 5th postoperative day and was not associated with infarction of either the nerve or its nuclei. Consequently, the presence of a 3rd nerve palsy was not considered indicative of vascular insufficiency and was discounted from the neurologic evaluation for purposes of this experiment.

The dogs were distributed among 3 groups: *I. Seven control dogs*, 3 dogs that had no surgery (1 normothermic, 2 hypothermic), and 4 dogs that had sham operations during which the artery was isolated but not occluded (3 normothermic, 1 hypothermic); *II. Fifteen dogs*, in which the left middle cerebral artery was interrupted at normal body temperature; and *III. Fifteen dogs*, in which the left middle cerebral artery was interrupted during hypothermia.

RESULTS

Group I. Controls. In order to evaluate the lesions in the brains of the experimental animals, it was necessary to differentiate between damage caused by vascular insufficiency and that produced by operative trauma. The latter was defined by study of the sham-operated controls; the results are listed in Table 1. Posttraumatic changes were generally found over the

TABLE 1

Normothermic and hypothermic controls

Dog	Procedure	Results	Neurological Score
2545	Normothermia, no operation	Normal brain	0
2401	Normothermia, sham operation	Posttraumatic changes pyriform lobe, olfactory peduncle, and sylvian gyrus	0
2422	Normothermia, sham operation	Posttraumatic changes pyriform lobe, olfactory peduncle, sylvian, ectosylvian, and suprasylvian gyri	1
2459	Normothermia, sham operation	Posttraumatic changes pyriform lobe, olfactory peduncle, sylvian, ectosylvian, and ectolateral gyri	0
2635	Hypothermia, 23.0°C., no operation	Normal brain	0
2693	Hypothermia, 22.5°C., no operation	Normal brain	0
2741	Hypothermia, 23.8°C., sham operation	Posttraumatic changes pyriform lobe, sigmoid gyrus	0

lateral aspect of the cerebral hemisphere subjacent to the edge of the craniectomy defect or line of dural closure and at the site of retraction of the pyriform lobe and olfactory peduncle. Allowances were made for these changes in the determination of the amount of destruction attributable to vascular insufficiency alone. The results recorded in Tables 2 and 3 list only pathologic alterations caused by the process of infarction.

No abnormalities were found in the brains of the 2 dogs subjected to hypothermia without operation.

Group II. Interruption of the Middle Cerebral Artery at Normal Body Temperature. The left middle cerebral artery was interrupted at its origin in 15 normothermic dogs. This was accomplished by 3 different procedures: simple transection, "crotch isolation," and segmental resection. The extent

TABLE 2

Interruption of the middle cerebral artery at normal body temperature

Dog	Procedure	Results	Neurological Score
2384	Transection	Infarction putamen, globus pallidus, int. capsule, caudate n., optic tract, amygdala, thalamus (lat., vent., dorsomed. n.), hypothalamus (fornix, lat., tuberal, periventricular n.), subthalamus, sylvian and suprasylvian gyri	15
2439	Transection	Infarction putamen, globus pallidus, int. capsule, caudate n., optic tract, thalamus (lat., vent., dorsomed n.), hypothalamus (lat., tuberal n.), sylvian gyrus	15
2473	Transection	Infarction putamen, globus pallidus, int. capsule, optic radiation, caudate n., centrum semiovale, amygdala, thalamus (ant., lat., vent., dorsomed. n.), subthalamus, hypothalamus (lat. n., fornix), sylvian, suprasylvian, and ectosylvian gyri	15
2555	Transection	Infarction putamen, globus pallidus, int. capsule, caudate n., thalamus (lat., dorsomed. n.), sylvian gyrus	7
2582	Transection	Infarction putamen, globus pallidus, int. capsule, caudate n., optic tract, amygdala, thalamus (lat., ant., vent., dorsomed. n.), subthalamus, hypothalamus (lat. preoptic area), ant. commissure	15
2594	Transection	Infarction globus pallidus, int. capsule, caudate n., optic tract, hypothalamus (lat. n.)	10
2700	Transection	Infarction putamen, globus pallidus, int. capsule, caudate n., centrum semiovale, corpus callosum, amygdala, thalamus (lat., vent. n.), sylvian, and coronal gyri	15
2715	Transection	Infarction putamen, globus pallidus, adjacent int. capsule, optic tract	0
2764	Transection	Infarction globus pallidus, int. capsule, amygdala, centrum semiovale, thalamus (lat., vent. n.), subthalamus, hypothalamus (fornix, mammillothalamic tract, tuberal, ventromed., lat. n.)	6
3002	Transection	Infarction putamen, globus pallidus, int. capsule, caudate n., optic tract, centrum semiovale, amygdala, thalamus (lat., vent. n.), hypothalamus (lat. preoptic, supraoptic areas, lat., tuberal n.), sylvian gyrus	11
2779	Crotch Isolation	Infarction globus pallidus, caudate n., int. capsule, optic radiation, thalamus (lat., ant., vent. n.), subthalamus	12
2867	Crotch Isolation	Infarction putamen, globus pallidus, int. capsule, amygdala, optic tract, thalamus (lat. n.)	13
2900	Resection	Infarction putamen, globus pallidus, int. capsule, caudate n., amygdala, thalamus (lat., ant., vent. n.), optic radiation	12

TABLE 2 (*Continued*)

Dog	Procedure	Results	Neurological Score
2904	Resection	Infarction putamen, globus pallidus, int. capsule, caudate n., amygdala, hypothalamus (lat. area), thalamus (lat., ant., vent., ventromed. n., pulvinar, lat. geniculate body), optic radiation, subthalamus	15
2908	Resection	Infarction putamen, globus pallidus, int. capsule, caudate n., amygdala, hypothalamus (lat. area), thalamus (lat., vent., dorsomed. n., pulvinar, lat. geniculate body), optic radiation, sylvian, suprasylvian, and ectosylvian gyri	15

of neurological disability and the severity of infarction are indicated in Table 2. All animals showed gross or microscopic evidence of infarction.

The 10 animals which had transections only could be separated into two subgroups. One-half of the dogs showed marked abnormal neurological signs, a score of 15; the other one-half showed lesser degrees of involvement, scores from 0–11. In general, the severity of pathological change was commensurate with the neurological manifestations. Fig. 2 demonstrates the extent of infarction in the brain of one of these animals.

"Crotch isolations" were done in 2 dogs in an attempt to produce more extensive lesions. However, the addition of secondary occlusion of the internal carotid, anterior cerebral, and posterior communicating arteries to transection of the middle cerebral artery did not appear to alter appreciably the neurological picture, either clinically or pathologically. Therefore, the number of animals in this portion of the series was not increased.

Three dogs were subjected to segmental resection of the middle cerebral artery from its origin to the first major cortical bifurcation. This effectively excluded sources of collateral circulation from meningeal anastomoses distal to the site of transection. Thus, precapillary and capillary anastomoses remained as the only points for establishment of collateral flow.[1] These animals showed more extensive necrosis than the other two groups. This is additional evidence that the meningeal anastomoses may be an important source of collateral circulation in the presence of a vascular occlusion.[19]

Group III. Interruption of the Middle Cerebral Artery during Hypothermia. A preliminary survey had indicated that cerebral infarction was prevented or diminished, when middle cerebral artery occlusion occurred at 25°C.[15] In an attempt to produce complete protection, the temperature range for these experiments was lowered to 22–24°C. At these temperatures, cerebral metabolism is probably 15–25 per cent of the pre-cooling rate.* The total period of hypothermia following the interruption of the vessel was 3 hours. Only the first hour was spent in deep hypothermia, 22–24°C.; the

* An extrapolation of the data from Rosomoff and Holaday.[17]

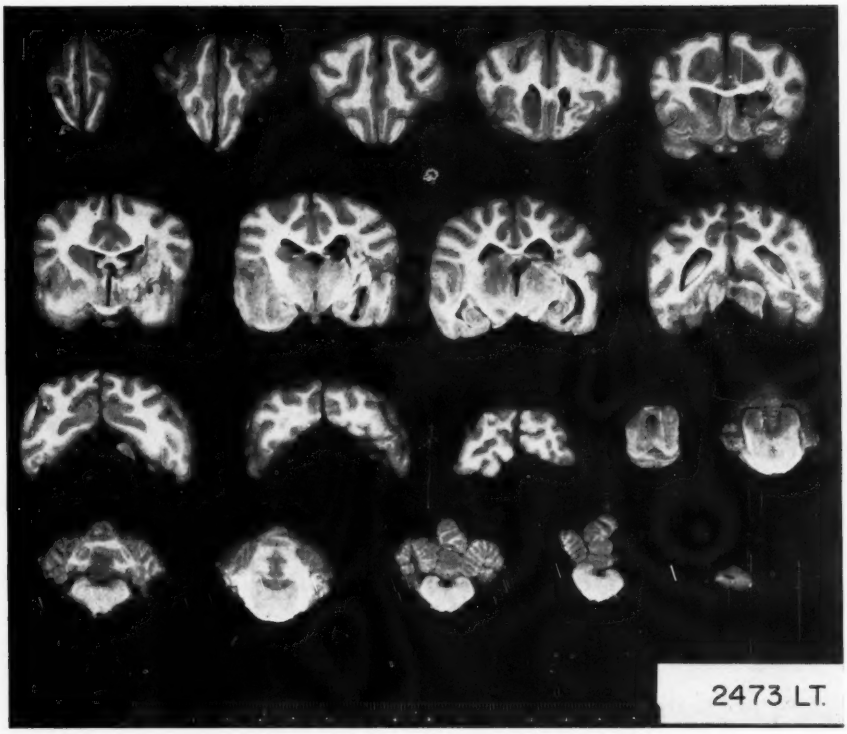

FIG. 2. Coronal sections of a dog brain following transection of the left middle cerebral artery at normal body temperature.

remaining 2 hours were spent at increasingly higher levels as part of the rewarming phase.

Again, the animals were divided into 3 groups—those that had transections, "crotch isolations," and segmental resections. Results are tabulated in Table 3. A comparison of the hypothermic dogs with their normothermic equivalents revealed a distinct difference. Clinically, only 5 of the 15 hypothermic dogs evidenced abnormal neurological signs. When such signs were present, they were minimal in degree, scores of 1 or 2, and transient, none persisting past the 6th postoperative day. In the remaining 10 animals no demonstrable clinical abnormalities developed.

Postmortem studies revealed a higher incidence of pathological change than would have been predicted from the dogs' clinical appearance. In all but 2 animals there was evidence of infarction; however, these infarcts were small, some being detectable only on microscopic examination. The paucity of clinical manifestations can be explained by their small size and by restric-

TABLE 3

Interruption of the middle cerebral artery during hypothermia

Dog	Procedure	Temp. °C.	Results	Neurological Score
2315	Transection	23.2	Infarction, 3×5×4 mm. (putamen, globus pallidus, caudate n., int. capsule, and lat. preoptic area)	2
2522	Transection	23.0	Infarction, 1×2×4 mm. (centrum semiovale)	0
2524	Transection	24.0	Infarction, 1×6×7 mm. (hypothalamus—lat. and med. preoptic areas, paraventricular n.)	0
2585	Transection	23.5	Infarction, 1×2×6 mm. (centrum semiovale, lat n. of thalamus)	1
2632	Transection	22.5	No infarction	0
2662	Transection	23.5	Infarction, 1.5×2×10 mm. (centrum semiovale), 2×1×10 mm. (int. capsule), 0.5×0.5×0.5 mm. (med. preoptic area)	1
2663	Transection	22.5	No infarction	0
2684	Transection	23.0	Infarction, 5×7×10 mm. (putamen, globus pallidum, int. capsule, vent. n. of thalamus)	0
2796	Transection	23.0	Infarction, 5×7×10 mm. (int. capsule, hypothalamus—fornix, med. preoptic area, paraventricular n., thalamus—ant., dorsomed. n.)	0
2840	Transection	22.0	Infarction, 5×7×10 mm. (thalamus—ant., lat., vent., dorsomed. n.), 2×3×8 mm. (globus pallidus)	0
2800	Crotch Isolation	22.5	Infarction, 1.5×3×8 mm. (hypothalamus—med. preoptic area; post., ventromed. n.)	0
2853	Crotch Isolation	22.5	Infarction, 4×6×8 mm. (globus pallidus, lat. hypothalamic and preoptic areas, pyriform lobe), 2×2×4 mm. (int. capsule)	0
2883	Resection	23.0	Infarction, 4×8×10 mm. (putamen, globus pallidus, amygdala, insula, adjacent int. capsule)	0
2909	Resection	22.5	Infarction, 7×9×10 mm. (putamen, globus pallidus, amygdala), 4×2×10 mm. (int. capsule, lat. hypothalamic area), 6×3×15 mm. (centrum semiovale, optic radiation), 3×3×15 mm. (thalamus—dorsomed. n., pulvinar, lat. geniculate body)	2
2913	Resection	22.2	Infarction, 8×10×10 mm. (putamen, globus pallidus, amygdala, adjacent int. capsule), 3×3×5 mm. (dorsomed. n. of thalamus)	2

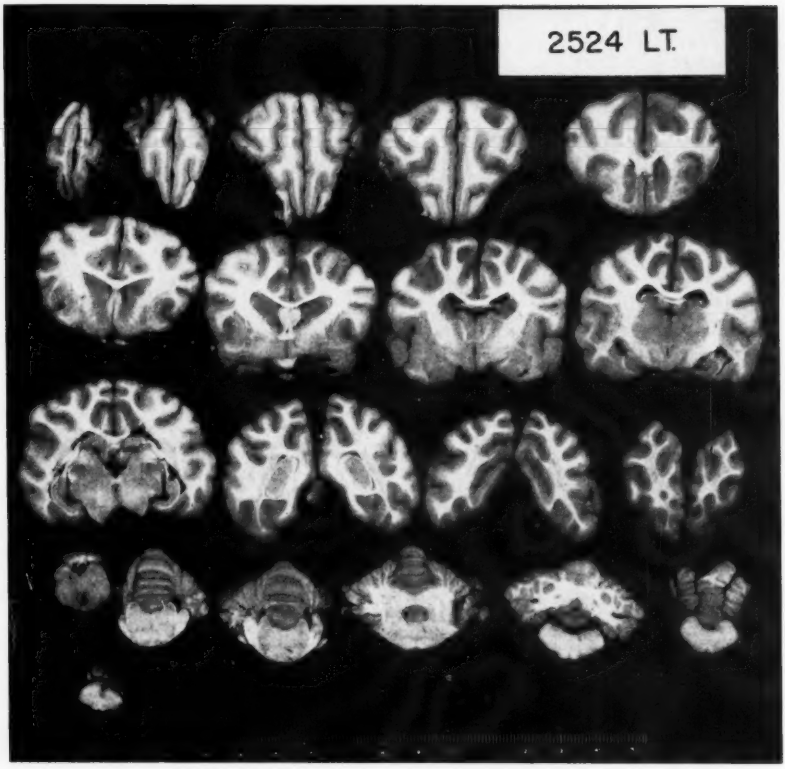

FIG. 3. Coronal sections of a dog brain following transection of the left middle cerebral artery during hypothermia.

tion of the lesions to relatively "silent areas"; i.e. portions of the basal ganglia, anterolateral internal capsule or thalamus, and hypothalamus. A sectioned hypothermic dog brain is shown in Fig. 3 in which such a lesion was found in the hypothalamus. In addition, there is a subcortical cyst in the left pyriform lobe of this brain which is traumatic in origin.

As in the normothermic groups, there was little difference in the changes produced in the transection series when compared with the "crotch isolations."

The segmentally resected animals had more extensive lesions than either of the other two groups, but not large enough to be clinically more significant.

Fig. 4 demonstrates the sharp contrast observed when coronal sections from the brains of normothermic dogs were compared with equivalent sections from the brains of hypothermic dogs following interruption of the left middle cerebral artery.

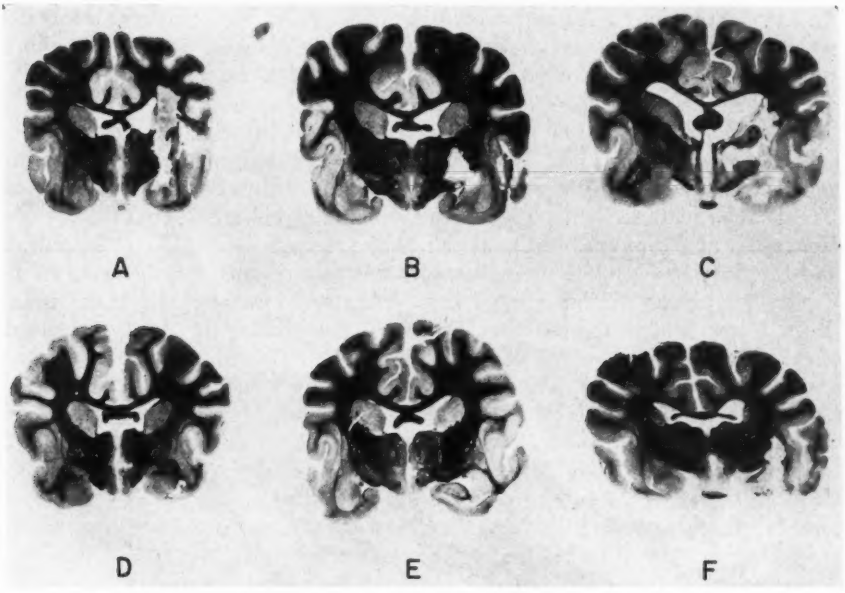

FIG. 4. Comparison of the severity of infarction following interruption of the left middle cerebral artery in normothermic and hypothermic dogs. *Upper row.* Normothermic. A, 2473 (transection). B, 2867 (crotch isolation). C, 2908 (resection). *Lower row.* Hypothermic. D, 2524 (transection). E, 2853 (crotch isolation). F, 2883 (resection).

DISCUSSION

Early anatomists had demonstrated a regular distribution and orderly arrangement of cerebral blood vessels.[2,5,18] They also described a lack of anastomoses between the terminal beds of penetrating arteries. This gave rise to the concept of "end arteries." More recent investigators have refuted this concept and have stated that anatomically there are no "end arteries" in the brain.[3,4,7,12,13,20] Anastomoses have been found over the meningeal surface of the brain as well as among the precapillaries and capillaries of the terminal areas of distribution.[1,19] It has been suggested that such anastomoses might have a significant potential for shunting a capillary bed from one source of supply to another in the face of a vascular occlusion, if such a shift were slow and over a sufficiently long period of time.[10]

Such an effect might be achieved in either of two ways. One, the main stem artery could be occluded slowly so that its collateral circulation has an opportunity to develop, as is seen in some cases of obliterative vascular disease in the extremities; or two, the metabolism of the part could be markedly reduced at the time of occlusion so as to minimize any disproportion between supply and demand. If then metabolism were restored, and collateral blood flow were established at a proportionate rate, no infarction would occur. The second approach appeared to be more suitable for application to the brain.

The morphologic studies had shown the existence of a potentially adequate collateral circulation, and a method of reducing cerebral oxygen consumption had been demonstrated with the use of hypothermia.[17]

The results of these experiments indicate that cerebral infarction in the dog was diminished or prevented when interruption of the middle cerebral artery occurred at 22–24°C. Protection was found not only with the transection procedures, but also following segmental resection of the artery. In the latter instance, the possibility of developing collateral blood flow from meningeal anastomoses was removed. The anastomoses of the precapillary and capillary beds then remained as the only source of collateral circulation. Under conditions of this study, these collaterals alone proved adequate. Thus, it was demonstrated that the brain does have the ability to shunt blood flow from one source of supply to another in sufficient quantities to maintain functional integrity, provided the proper set of circumstances is established. This is offered as additional evidence that "end arteries" do not exist in the brain.

The most immediate clinical application of this information is likely to be found in the field of neurological surgery. The operative treatment of cerebral vascular anomalies is particularly hazardous because of the risk of producing a neurological deficit consequent to the deliberate or accidental interruption of a major vascular channel. The use of hypothermia may make it possible to avoid this catastrophe, thereby allowing the treatment of a greater number of these patients. In addition, hypothermia provides several advantages which are applicable not only for operations of vascular lesions, but to other forms of intracranial surgery as well. These include a reduction in cerebral blood flow which facilitates hemostasis,[17] a decrease in brain volume which enhances surgical exposure, and a diminution of intracranial pressure.[16] Thus, the use of hypothermia promises to enlarge the scope of neurological surgery, as well as to provide an additional tool for the study of cerebral function both in health and disease.

SUMMARY AND CONCLUSIONS

The middle cerebral artery of the dog was interrupted at normal body temperature and during hypothermia. Each normothermic dog developed a cerebral infarct. When interruption of the artery occurred at 22–24°C., either no infarct developed or lesions were found which were small in size and restricted to relatively "silent areas." It was concluded, therefore, that hypothermia protects against cerebral infarction in the dog following interruption of the middle cerebral artery.

The author is indebted to J. Ewell, HM3, USN, for his valuable assistance during the course of these experiments. Gratitude is also expressed to Mrs. A. B. Snodgress and her staff for the preparation of the histologic material from this study, and to W. B. Heymann, HMC, USN, and M. H. Rhodes, HMC, USN, and their staff for photographic support.

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SCINTISCANNING AS A METHOD FOR LOCALIZATION OF CEREBRAL TUMORS*

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SINCE Moore[5] introduced radioactivated diiodofluorescein as an aid in the diagnosis and localization of intracranial tumors, there have been numerous attempts to perfect a method whereby such tumors may be localized with accuracy, facility, and without mortality. Belcher,[2] using this labeled chemical and a similar technique, was able to localize only 1 out of 20 verified intracranial tumors. Later Peyton *et al.*[6] as well as Dunbar and Ray[3] reported the use of iodinated serum albumin (RISA). Counting rates indicative of variable uptakes in tumors were observed. The impression was gained that uptake of serum albumin was best detected in tumors in which there was increased vascularity or increased capillary permeability. Evidence indicative of radioactive substances entering the cells was not demonstrable.

For a period the procedures for localization were encumbered by multiple point counting techniques such as suggested by Langer and Loevinger.[4] Subsequently Sweet and Brownell[7] reported a system of scanning in a horizontal plane and localized tumors with acceptable accuracy. The disadvantages of their method were: the initial expense of equipment, complexity of operation, and the need to be near a source of As^{74}. Allen and Risser[1] described a refinement in technique by lowering the laboratory background count and selecting only the harder portion of the spectrum of I^{131} for analysis. This method is in need of further investigation.

In reviewing the literature on the subject of brain tumor localization with the labeled iodine technique, it became apparent that a method was needed to use material that was readily available and to employ simple technical aids. By accomplishing this, intracerebral tumors could be scanned at modest facilities and by personnel having a limited experience in electronics and physics. Toward this end a scintiscanner has been designed (Fig. 1) which has necessitated structural modification of an automatic scanning device primarily used for scanning of the thyroid gland.

The head of the scintillation detector consists of a magnetic and lead shield which is divided into two parts. The crystal is a Harshaw thallium activated sodium iodide crystal, 3″ in diameter and 1″ in thickness. The crystal is coupled with a suitable

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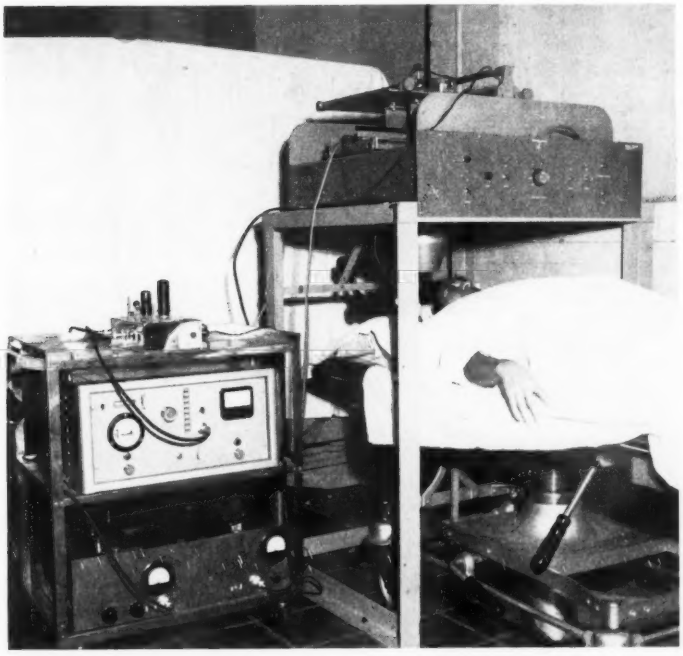

FIG. 1. General view of the scintiscanner showing the patient beneath the focusing collimator.

cone of lucite to a RCA 6199 photo-multiplier tube. This tube feeds into a preamplifier, thence to a pulse amplifier which is coupled to a power amplifier which drives a cold cathode modulator tube. The glow modulator tube output may be recorded on photographic paper (Fig. 2). Collimation is selected to achieve maximum resolution

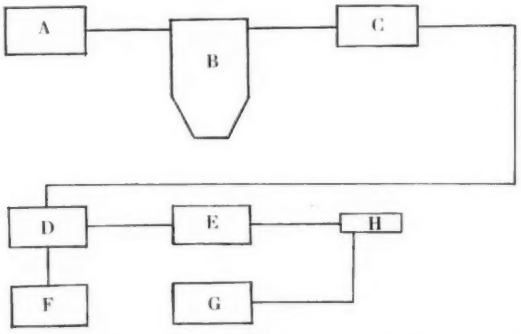

FIG. 2. Schematic of the circuit. (A) High voltage supply. (B) Detector. (C) Pre-amplifier. (D) Pulse amplifier. (E) Power amplifier. (F) 150-volt regulated power supply. (G) 300-volt regulated power supply. (H) Light source.

in the 3.5″ plane distal to the nose of the detector. This is obtained by choosing a shield having a 20° cone. The channels themselves have a width of 3/16″. From the diagram (Fig. 3) it is readily appreciated that there is a cone of 20° of radiation dead space. This has been established by measurement of sources at the 3.5″ plane and for distances less than this. Because of the width of this angle and the restricted collimation, the probability of the detector "seeing" a superficial vascular pool in the scalp, diplöe, or cerebral cortex instead of a concentration in a deeply seated tumor is considerably diminished. In other words, the detector sees unequally at superficial levels while scanning to depth. Discrimination has not been employed to eliminate secondary radiation since deep tumors frequently exhibit considerable low energy phenomenon because of the Compton effect. The pulses received by the scaler may be recorded by statistical overprint with a telegraphic printer, a photo overprint using a Sylvania R 1131C tube, or by photoprinting with the frequency sensitive circuit previously described.

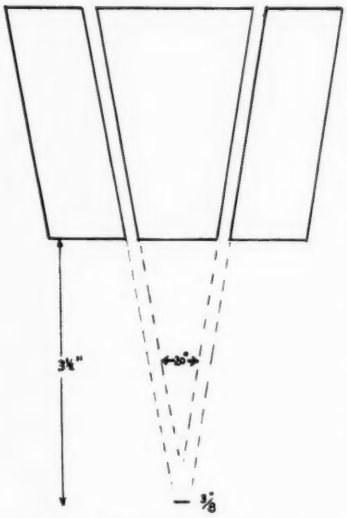

FIG. 3. Diagram of the focusing collimator.

The material studied in this clinic has been, for the most part, gliomas of the cerebrum. Patients are prepared by blocking the thyroid gland by the oral administration of Lugol's solution followed by an intravenous dose of RISA (300–500 μc). Scanning is performed 24–48 hours later. Abnormal uptakes in the cerebrum on the side of the tumor have been found to occupy specific areas of the neoplasm. Sharp borders of the tumors have seldom been recorded, apparently because of regional necrosis of the brain and/or irregular invasion of adjacent tissue by the neoplasm.

Scanning to depth may be employed to advantage in examples of intracerebral tumors provided these lesions exhibit increased vascularization. This is especially true of neoplasms within the posterior cranial fossa. Here the overlying musculature and the great depth of the potential lesion make many methods of detection useless. Sweet and Brownell[7] have stated that neoplasms of the posterior fossa elude diagnosis with I^{131}, K^{42}, and As^{74}, because of the masking effect of the overlying muscles. In our clinic, 3 out of 4 verified posterior fossa tumors were identified conclusively using our present technique, as described. Two of these were medulloblastoma and one was an angiomatous meningioma (Fig. 4). The remaining patient had a vascular malformation which was not detected. More recently, the circuit has been modified to record a "negative" print and using this technique an arteriovenous malformation of the frontal lobe of the left cerebral hemisphere has been recorded (Fig. 5).

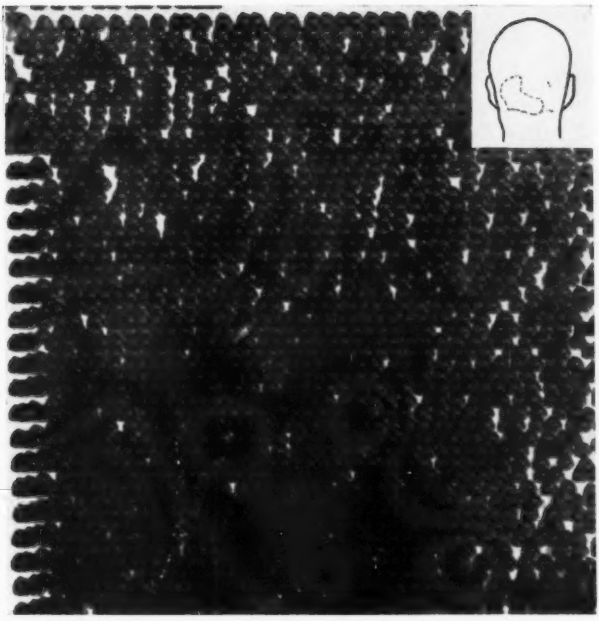

FIG. 4. Positive print of a case of angiomatous meningioma of the posterior cranial fossa. This scan is in the posterior-anterior orientation of the head. The areas of increased density correspond to the localization pictured in the small diagram.

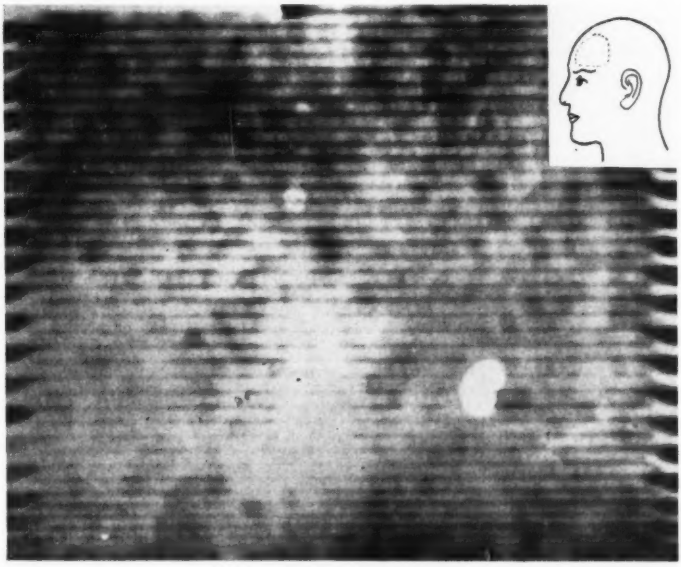

FIG. 5. Negative print of a case of an angiomatous malformation of the left frontal area of the cerebrum as viewed in the left lateral position of the head. The area of greatest activity is represented by the absence of printing.

SUMMARY

A technique for automatic scanning of the head after intravenous injection of radioactivated iodinated human serum albumin has been described which has been successful in the localization of various types of brain tumors. This localization has been made possible by directional detection and a moderately sensitive recording device. It is hoped in the near future that the method will become effective for a greater variety of neoplasms by using a more sensitive electronic circuit and a more specific tumor metabolite.

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CONTRAST MEDIUM INJURY TO THE SPINAL CORD PRODUCED BY AORTOGRAPHY

PATHOLOGIC ANATOMY OF THE EXPERIMENTAL LESION*

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THE acute pathologic changes in the central nervous system produced by intracarotid injection of toxic doses of contrast media in experimental animals are well known. The mildest lesion consists of a transient breakdown of the blood-brain barrier, demonstrable only by the use of dye indicator technics, and unaccompanied by other structural changes.[8,38] Reactions of greater severity are manifested by edema, vasodilatation and stasis, and by punctate hemorrhages.[3,4,7,9] Anatomic evidence of neuronal damage has been sparse, only a single experimental study reporting a significant structural change.[4] This effect, seen in acute experiments productive of severe disturbances in cerebral electrical activity and of the toxic manifestations listed above, consisted of an advanced hydropic cytoplasmic degeneration of neurones. Other than this report, there is no evidence from experimental studies to suggest that the contrast media are capable of producing an irreversible neuronal lesion.

Beyond the immediate and acute pathologic changes resulting from contrast medium injury in animals, virtually nothing is known. The reported experimental studies have made no attempt to follow the complete evolution of the lesion, or even to allow sufficient time for the necrobiotic and reactive changes secondary to irreversible tissue injury to appear. That negative results have been obtained in chronic studies[16,23] merely indicates that an irreversible lesion was not produced in such experiments. The scarcity of chronic studies may reside in part in the general focusing of interest upon the initial stages of the reaction, and in part in the inability of the severely brain-injured animals to survive beyond the acute phase of the injury. Recently, however, a method has been developed for the production of a central nervous system injury by contrast media allowing extended survival of the injured animals and providing an opportunity for the functional and anatomic study of all temporal phases of the contrast medium lesion. The anatomic features of the cord injuries are described in the present report.

* Presented at the meeting of the Harvey Cushing Society, Quebec, Canada, May 18, 1955.

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PROCEDURES AND GENERAL RESULTS

These have been reported by us elsewhere,[42] but it is necessary to summarize them in detail here.

The method of injury consisted of the rapid intra-aortic injection of 7 to 20 cc. (approximately 1 cc. per kg.) of a contrast medium into dogs. Except for a few studies made with 70 per cent Diodrast[R] (diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid) the contrast medium used was 70 per cent Urokon sodium[R] (3-acetyl-amino-2-4-6-triiodo sodium benzoate).* The injections were made at one of three levels: just below the renal arteries, above the superior mesenteric artery, or in the mid-thoracic aorta. An 18-gauge needle was used, pointing obliquely cephalad, and the injection was given over a 5 to 10 sec. period. In all injections, the animal was anesthetized with Nembutal and the aorta was surgically exposed. In the mid-thoracic injection, the animals were positioned on their right side; otherwise they were in a supine position. A total of 41 dogs was used in these experiments; the animals were sacrificed at periods varying from 5 hours through 27 days following the injection.

At the conclusion of each study, the animal was sacrificed by an overdose of Nembutal, and the vertebral column was removed. The entire cord was exposed by a dorsal laminectomy and fixed in situ for a few hours in isotonic neutral formalin, following which it was removed and fixation was completed with the cord suspended in a 5000 cc. cylinder. Most of the cords were sectioned transversely at 0.3 to 0.5 cm. intervals, but a few cords were sectioned longitudinally in a horizontal plane. The gross features of the lesions were recorded and in some instances photographed. Sections at 1.5 cm. intervals from the caudal 15 cm. of cord and from other levels with grossly recognizable lesions, and at 5 cm. intervals from the remainder of the cord were chosen for microscopic study. The materials were embedded in paraffin and sectioned at 6 microns. The sections were routinely stained with hematoxylin-eosin and with a modification of the Klüver-Barrera stain developed in our laboratory.[30] This method, which allowed a study of the cell picture, the myelin sheath pattern, and the vascular bed in a single preparation, consisted of Luxol fast blue MBS (du Pont) followed by the periodic acid-Schiff reaction and a hematoxylin nuclear stain.

As a correlative study the acute phases of the cord injury were compared with lesions encountered in a previous study evaluating certain contrast media used for cerebral angiography[4] and observed only in their early stages of development. The cerebral lesions had been produced by the following agents: Diodrast 35, 50, and 70 per cent; Neo-iopax[R] (3,5-diiodo-4-pyridoxal-N-methyl-2-6-carboxylic acid) 37.5 per cent; N-methyl nicotinamide hydrochloride 20 per cent, a normal body metabolite approaching the chemical structure of these agents; Urokon 30 per cent at pH 5.4 and 7.0; its non-iodinated homologue, 3 acetylaminobenzoic acid 20 per cent at pH 7.4; and the benzene derivative para-aminohippurate 20 per cent.

During these studies it soon became evident that anatomic features such as the blood supply of the spinal cord and its caudad position were of prime importance in determining the site and severity of the contrast medium lesion. Accordingly, a special study of these relationships was made in 14

* Kindly furnished by Mallinckrodt Chemical Works, St. Louis, Missouri.

of the dogs. The aorta was left attached to the vertebral column when it was removed, and the approximate level of injection was indicated by an India ink marker on the exposed dura mater. Following this, the arterial circulation was plotted under a dissecting microscope, with particular attention directed toward the distribution and relative size of the radicular arteries. The blood supply was found to be essentially similar to that of the human cord,[41] with a relatively rich lumbosacral and cervical radicular supply and a poorer thoracic supply. It was also observed that the canine cord extended to the level of the 7th lumbar vertebra. Thus, a long stretch of the cord richly vascularized by short dorsal branches of the abdominal aorta was maximally exposed to the contrast medium. This exposure was graphically demonstrated by roentgenological studies made in selected animals, recording the position of the needle and the flow and distribution of the contrast medium during the terminal portion of the injection. The single roentgen-ray exposure made at the terminal phase of the injection showed only rarely the flow of the contrast medium into the spinal cord circulation. However, it did provide an adequate picture of the distribution of the injected material, particularly a retrograde flow extending rostrally the distance of one or two verebral bodies, and a filling of the dorsal branches of the aorta. Examples of these studies correlating the level of the injection and the initial flow of the contrast medium with the blood supply and the site of the lesion may be found in our other communication.[42] These topographic features are so intimately related to a consideration of the pathologic anatomy of the contrast medium lesion that they will be presented in detail below.

The modifying effects upon the lesion of variations in the amount and type of the contrast media and in the level of injection have been presented by us in detail elsewhere.[42] The effects may be summarized as follows: Urokon was more toxic than Diodrast. A halving of the dose did not significantly modify the severity of the reaction. And with high thoracic injections, the site of injury was sometimes centered in the thoracic cord rather than in the terminal portion; the cord lesions tended to be less severe, and in some specimens the injury involved the thoracic white matter more than the gray matter.

While this work was in progress, another report appeared of experimental contrast medium injury to the spinal cord.[19] This was an acute study in rabbits with the anatomic aspects limited to tests for a disturbance of the blood-brain barrier. One conclusion of interest drawn from this study was that an injection with the animal in the supine position favored dorsal filling and, hence, increased the chances of cord injury. This differential flow was explained on the basis of the specific gravity of the contrast medium being higher than that of blood. Accordingly, 6 animals were injected while in the prone position, with no paralyzing effects being encountered. These animals were not subjected to histologic studies.

A detailed description of the spinal cord lesion produced in our studies follows.

THE CONTRAST MEDIUM LESION

The functional effect of the contrast medium injection was expressed in the following characteristic manner: During the injection, a pronounced extensor rigor occurred, sometimes persisting as long as a minute. This reaction, considered to be comparable to the seizure discharges observed in experimental cerebral angiography,[4,8,9,14,38] was succeeded by a state of hyperirritability of a few minutes' duration. These spinal convulsions invariably augured the development of a severe paraplegia, often with a pronounced spastic component, which was evident in the lower legs and back upon recovery of the animal from the anesthetic. The characteristic anatomic effect produced by the injection consisted essentially of a destruction of the gray matter of the lower portion of the spinal cord. The resultant lesions were classified according to an arbitrary system separating the injuries into clearly defined categories of progressive severity, designated as follows:

\+ Sparsely scattered microscopic foci of destruction, affecting gray or white matter, present in one or more sections of spinal cord.

++ Multiple small (1–2 mm.) scattered foci of destruction of gray matter, with or without involvement of white matter or spinal nerve roots, distributed over 3 to 5 cm. of spinal cord.

+++ Massive focal discrete or confluent zones of destruction of gray matter with or without involvement of white matter or spinal nerve roots, extending over 5 to 10 cm. of spinal cord.

++++ Hemidestruction to complete devastation of gray matter, frequently extending deeply into the white matter and spinal nerve roots, involving from 10 to 18 cm. of spinal cord.

In 36 of the 41 animals tested there were cord lesions graded as follows:

+	5
++	9
+++	8
++++	14

In the description to follow, attention will be focused on injuries of the two most advanced grades.

The initial phases of the contrast medium injury were studied in 4 dogs, sacrificed 5 to 10 hours after the injection. The early stages of the injury were manifest in two forms. One of these was a massive hemorrhagic necrosis, rather sharply limited to the gray matter (Fig. 1A) observed in a dog sacrificed 10 hours following the injection. The terminal 10 cm. of cord was involved by this reaction. The parenchyma within and bordering the hemorrhage was strikingly edematous, and far advanced cytolytic changes had affected the neurones. The second type of early change was unattended by significant hemorrhage, and appeared as a profound edema. This change was observed in 2 dogs, sacrificed at 5 and 6 hours after the injection. In one, the alteration was so severe that the gross topographical features of

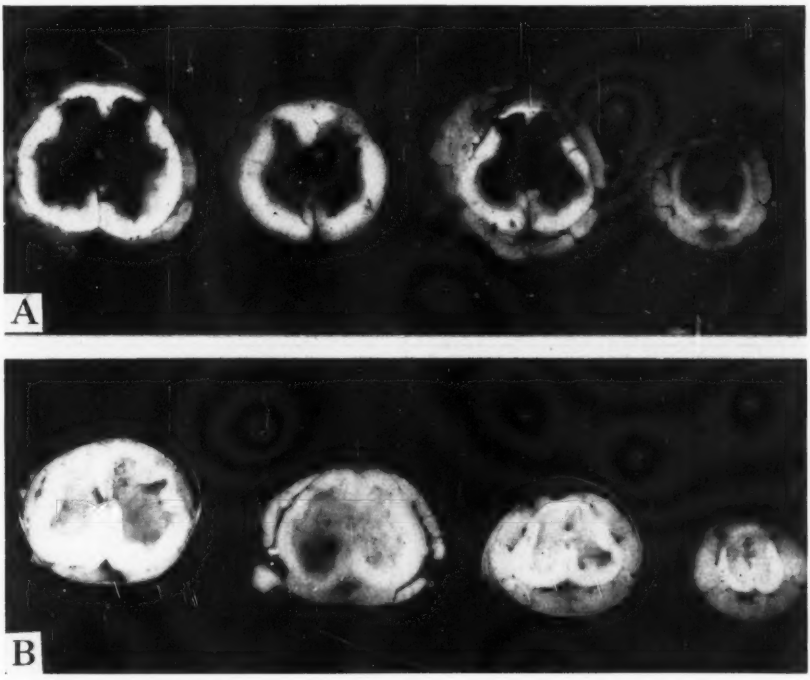

FIG. 1. (A) Lumbosacral segments of spinal cord 10 hours following Urokon injury. Massive hemorrhagic necrosis.

(B) Lumbosacral segments of spinal cord 6 days following Urokon injury. Early myelomalacic changes are confined essentially to gray matter. See Fig. 2B for microscopic appearance.

the sectioned cord were obscured over the caudal 15 cm. In microscopic preparations, a selective involvement of gray matter and a sparing of white matter were clearly demonstrated (Fig. 2A). Virtually all the neurones in the edematous zone had undergone a severe hydropic degeneration. The Nissl substance was lysed and the cytoplasm was honeycombed with vacuoles (Fig. 3A). The nuclei were less severely affected by karyolytic changes. Oligodendroglia exhibited a balloon-like swelling. At this stage the myelin network, even in the most severely involved areas, remained unaffected. The basement membrane of capillaries was still intact, but the small vessels of the cord were strikingly bloodless. No thrombotic features were observed, and larger vessels were not structurally altered. These early lesions were comparable to the most advanced changes produced by the various agents used in the previous contrast medium study.[4] Both of these sets of lesions presented a gross edema, severe hemorrhagic manifestations, and an advanced degree of cytolytic change in neurones, featured by hydropic degeneration and chromatolysis.

The continued development of the contrast medium injury was observed in 32 animals sacrificed at periods of 2 to 27 days following the injections. One animal studied at 2 days showed an extensive advanced edema and cytolysis. In a dog sacrificed on the 4th day, the cord was involved by a hemorrhagic necrosis which wiped out the gray matter of the caudal 13 cm. (Fig. 6B).

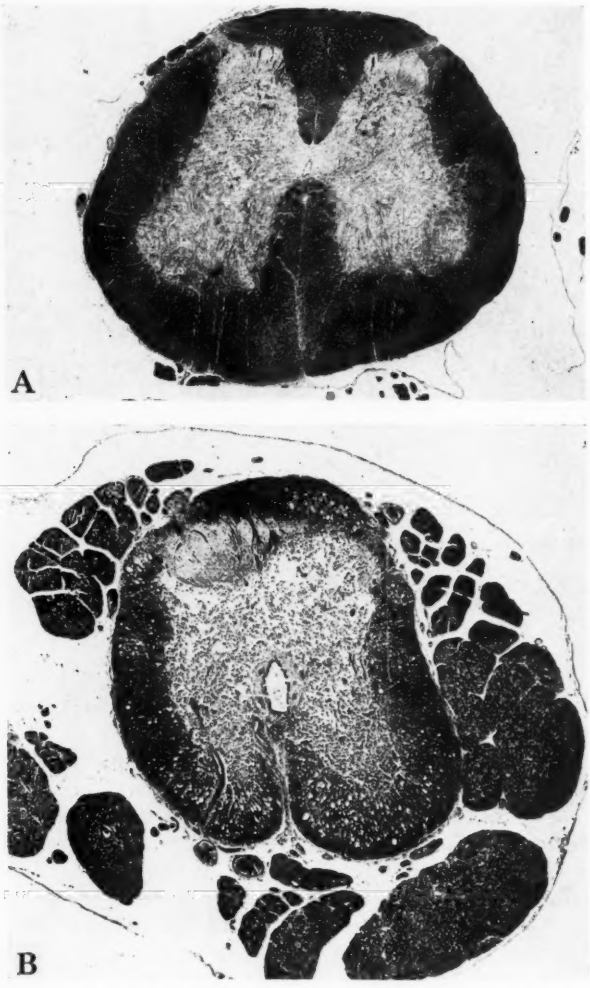

FIG. 2. (A) Lumbar cord 5 hours following Urokon injury. There is advanced edema involving entire gray substance and sparing white matter. Details of this lesion are shown in Fig. 3A. The normal density of gray matter may be seen in the right half of the cord in Fig. 4B. Modified Klüver-Barrera stain.

(B) Sacral cord 6 days following Urokon injury. Myelomalacia affects virtually all of gray matter; scattered degenerative changes are present in white matter. Modified Klüver-Barrera stain.

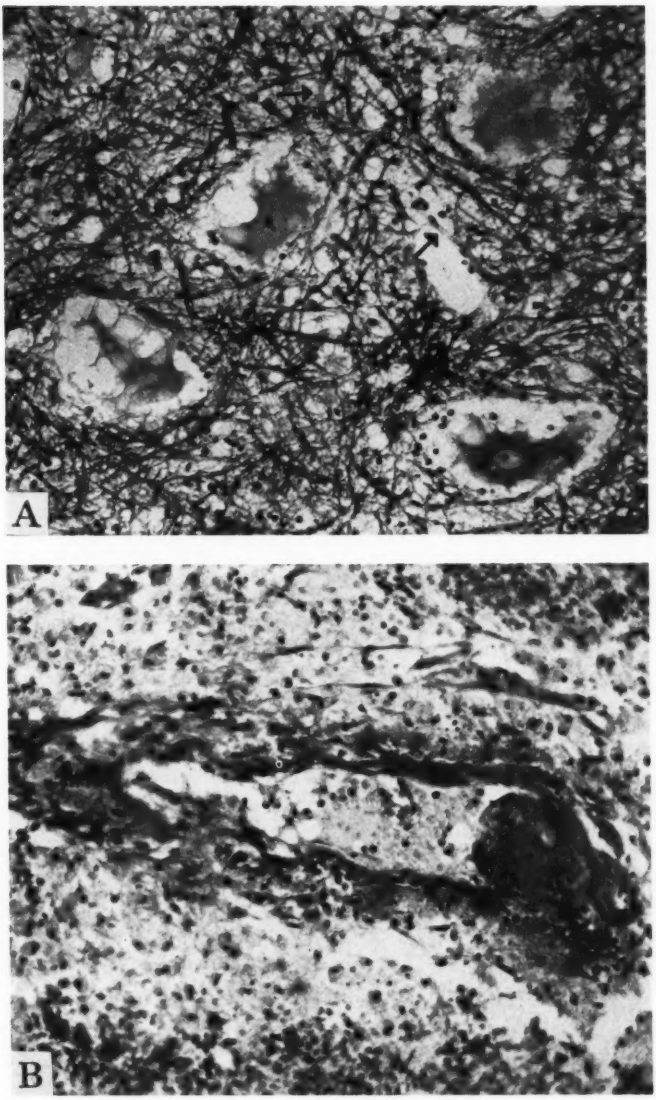

FIG. 3. (A) Gray matter 5 hours following Urokon injury. Note advanced cytolytic changes with hydropic degeneration of anterior horn cells and interstitial edema. The fiber network and capillary bed (arrows) appear structurally intact at this stage. For a colored plate of this figure see Fig. 5 of Margolis and Pickett.[30] Modified Klüver-Barrera stain, ×219.

(B) Main trunk of anterior sulcal artery just beyond point of entrance into spinal cord. Fibrinoid necrosis and secondary thrombus formation, 6 days following Urokon injury. Hematoxylin-eosin stain, ×219.

Virtually all the white matter in the segment of cord infiltrated by hemorrhage was bloodless and necrotic. In the remainder of the animals, studied at 6 days or longer following the injections, progressive disintegrative changes with resorption of the necrotic material and cavity formation constituted the outstanding features. As early as 6 days, the injured regions of the cord had become softened and spongy. The distribution of these changes, with the lesion being confined at a gross level to gray matter (Fig. 1B) was remarkably similar to the topography of the lesions studied at earlier stages.

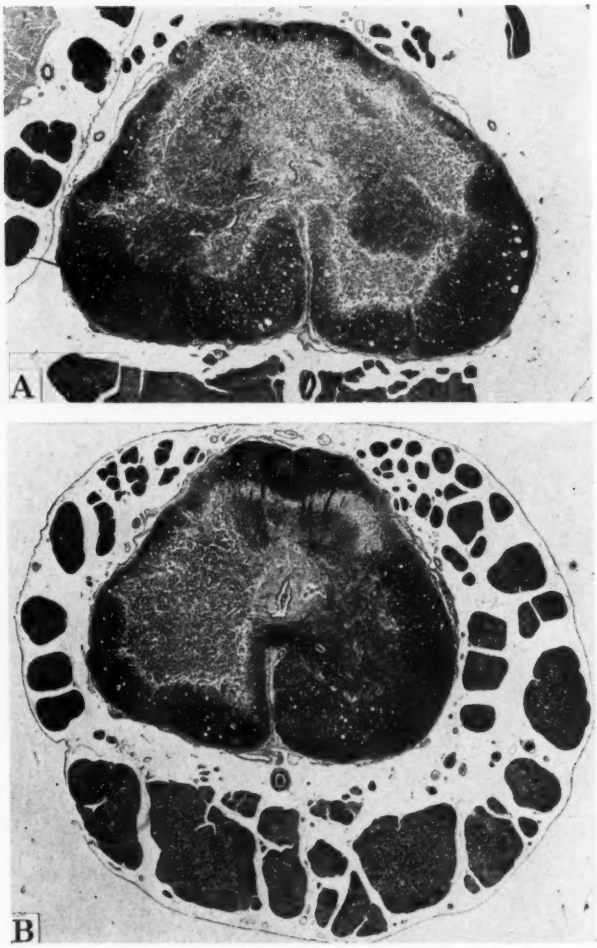

FIG. 4. (A) Lumbar cord 14 days following Urokon injury. Massive bilateral myelomalacia destroying all of gray matter and extensively involving white matter. Modified Klüver-Barrera stain.
(B) Sacral cord of same animal. Unilateral lesion involving supply zone of an anterior sulcal artery.

At a microscopic level, the destructive changes were centered upon gray matter (Fig. 2B) but not so sharply limited. Injury of the white matter was observed in the form of involvement of the lamina propria, scattered focal destructive changes, broad areas of extension into white matter closely approaching a transecting lesion (Fig. 4A), and focal destruction of spinal nerve roots.

The severe edema in all the early lesions and the few examples of massive hemorrhage are adequate indicators of a severe vascular injury. However, the structural integrity of the vascular network was preserved to a greater degree than the other fixed tissue elements. As indicated above, the capillary basement membrane appeared intact at a time when the neurones were irreversibly injured. At 5 to 6 hours most of the lesions appeared ischemic, but no thrombi were observed. At 2 days, the capillaries appeared generally intact, except for the presence of infrequent thrombi having the appearance of agglutinated platelets. In the material studied evidence of anatomical lesions in the vessels of the pia was rarely observed. In lesions at 4 days and later, a fibrinoid necrosis and associated thrombosis was occasionally observed in the largest intrinsic arteries of the cord, particularly the anterior sulcal artery just beyond its point of penetration into the cord (Fig. 3B). In the fully developed cystic lesions, a loose network of vessels spanned the cavities.

The histologic features of these fully developed lesions associated with cavity formation were characterized by the destruction of virtually all tissue components, including neurones, glia, and the vascular network as described above. The zones of destruction were sharply bordered, with an abrupt transition to normal tissue at their margins. Swarms of activated microglia, distended with lipids and other cellular debris, occupied the cavities. In the bordering tissue, a variable astrocytic proliferation was observed.

The topographic features of the lesions demonstrating the intimate relationship between the level of the injection, the initial distribution of the contrast medium, and the anatomical position and arterial supply of the spinal cord are graphically illustrated in Figs. 5, 6, and 7, correlating these studies in a single dog. Shown particularly well is the manner in which the cord injury following an injection into the abdominal aorta uniformly extended higher than the level of the injection, a distribution closely corresponding to the initial retrograde flow of the contrast medium in the aorta. Also clearly demonstrated is the low anatomical position of the canine cord which renders it so susceptible to injury in these procedures. The virtually selective involvement of gray matter may be explained in part by the differential vulnerability of this tissue and the richness of its blood supply. However, this localization also corresponds closely to the primary distribution of the sulcal branches of the anterior spinal artery,[18] a feature suggesting that the injury may be the result of the heaviest and most concentrated flow of contrast medium through this pathway. Support for this

concept is found in further topographic features of the lesions. In some cords, the injury had a remarkably unilateral distribution (Fig. 4B), and occasionally alternate sides were affected at different levels. Such lesions could be most readily explained on the basis of a direct injury to an anterior sulcal artery or its primary branches, or by the sweep of a substance of noxious character through this vascular network. Although thrombotic and necrotizing lesions were observed in this vascular bed, such lesions were infrequent.

FIG. 5. Lateral roentgenogram showing distribution of Urokon at terminal period of injection. Features to be noted include the retrograde flow and the filling of the dorsal branches of the aorta. However, it is clearly evident that the major portion of the contrast medium is destined for the circulation of the extremities.

In a few animals, distinctly demarcated zones of nearly complete destruction of gray matter were separated by a region with minimal involvement. No vascular maps enabling a precise correlation between blood supply and the site of the lesion were available in this group. In some cords, sharply focal lesions in gray matter again suggested an injury based primarily upon a

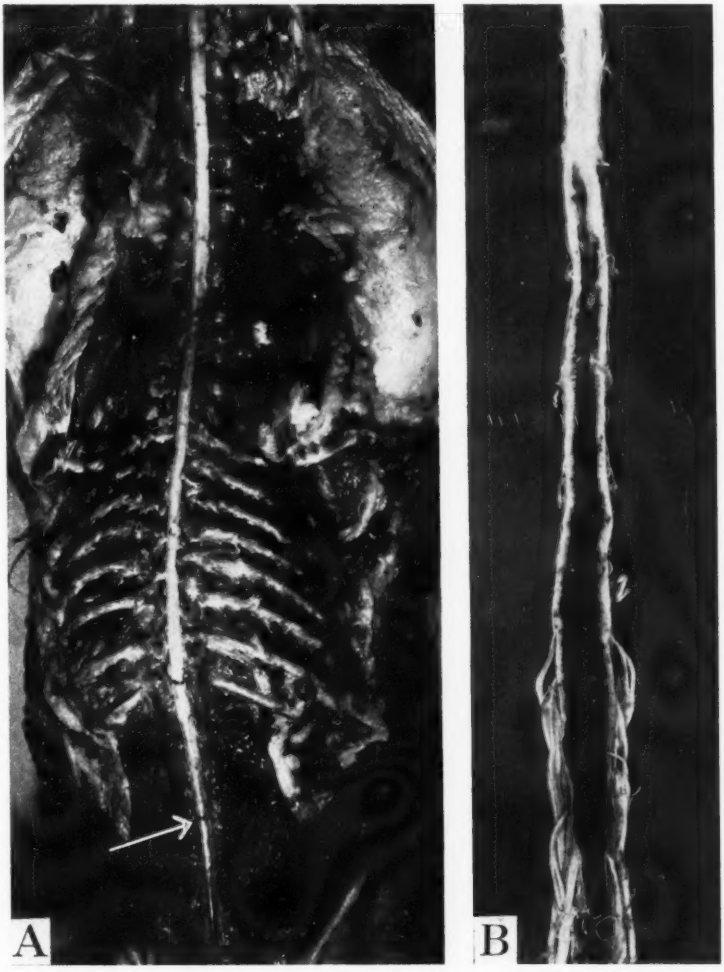

FIG. 6. (A) Dog with spinal cord exposed to demonstrate anatomic position. Twelve cm. of cord are situated below the level of T13. Four days previously this animal had been injected with Urokon into the aorta at a level of the 6 cm. below T13 (arrow indicates level).

(B) Longitudinal horizontal section through low thoracic lumbosacral cord. Massive hemorrhagic necrosis involving terminal 13 cm.

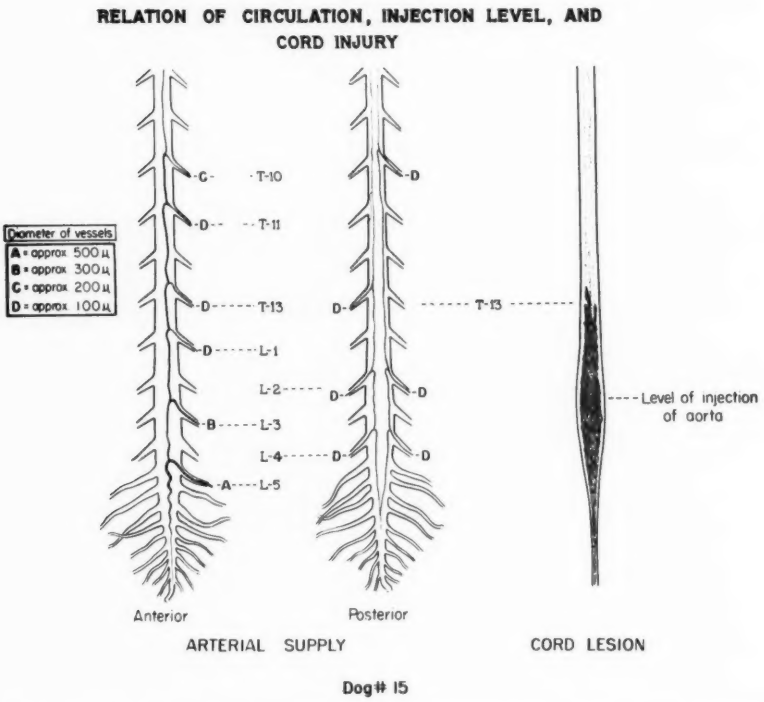

FIG. 7. Diagram showing relationship of circulation, injection level, and distribution of spinal cord injury in the animal pictured in Fig. 6. The approximate postmortem diameter of each radicular artery is designated by an appropriate letter, according to the classification indicated in the box.

direct effect upon the vascular bed. The preponderance of white matter involvement in the thoracic cord lesions pointed to the possibility of entry of the contrast media along posterior root radicles in this zone.[18]

DISCUSSION

The contrast medium lesion produced in these investigations is so far beyond the grade of injury previously observed in experimental studies of the effects of these substances that it compels a re-evaluation of the toxic potential of these agents. On the basis of these observations it is evident that the concept of the effect as a transient vascular disorder, exemplified by the statement of Broman and Olsson[9]

"... the injury caused by [Umbradil forte and Ioduron] being manifest solely as a ... completely reversible disorder of the vascular permeability without any attendant signs of edema, stasis, or hemorrhages. ... (It is conceivable that this effect may be of therapeutic value in certain diseases.)"

is no longer valid. It is evident from comparative studies of the acute phases of the spinal cord lesion and of previously observed experimental angiographic injuries of the brain that the reaction encountered in these studies is not to be considered as a new order of injury. Rather it is the natural evolution of the maximal contrast medium injury, followed through its complete developmental stages, observable only because the site of injury was compatible with extended survival of the experimental animals.

The objection may be raised that the injury encountered in these experiments is not comparable to that observed in other reported studies. Particularly, the argument may be advanced that factors such as size of dose, concentration of the medium, elevated intraluminal pressure associated with the rapid injection,[38] and a differential gravitational flow of the contrast medium resulting from the supine position of the animals during the tests[19] may have heavily weighted these studies in favor of a toxic effect far beyond that possible to achieve with other methods. The test dose, of approximately 1 cc. per kg. body weight, is comparable to that used in clinical angiography. Furthermore, it is clear from a study of the angiograms (Fig. 5) that only a small fraction of the injected material reaches the circulation of the spinal cord.

Our own experience[4] with the lesions produced by 30 per cent Urokon clearly demonstrates that the concentration used in these studies is far in excess of the critical level toxic for the nervous system. This observation is firmly backed by clinical studies.[31,36] No attempt was made to measure the degree of dilution of the contrast media in our studies. Information available in the literature points to a rapid dilution under such circumstances. Idbohrn and Jacobsson[21] reported a maximum concentration of 17 per cent in the contralateral femoral artery following the retrograde femoral injection of 60 per cent Umbradil[R] (20–50 cc. in 2 to 3 sec.) in rabbits. Fariñas[13] reported that the intra-aortic concentration following the injection of a small amount of 70 per cent Diodrast (20 cc. in 2.5 to 3 sec.) in man was 8 to 10 per cent. Idbohrn and Berg[20] found that 50 per cent Umbradil (3 cc. per kg.) injected into the carotid artery of rabbits was diluted to 19 per cent or less in the femoral artery. This high dilution factor may be used to justify the use of 70 per cent concentration of contrast media in clinical aortography. Yet Idbohrn and Berg reported renal injury by Umbradil at a critical level between 10 and 17.5 per cent.

The factor of increased intraluminal pressure is minimized by the large vascular bed into which the injection is made. Studies in our laboratories[29] have demonstrated no rise in intra-aortic pressure with these injections. Stirling[39] has demonstrated a rise of 8 mm. Hg in the aorta and 2 mm. Hg in the renal artery following the injection of 18 cc. of contrast medium in less than 1 second into the aorta of man.

It is an undeniable fact that the supine position during injection favors the production of spinal cord injury by a contrast medium. The radiographic studies of Hol and Skjerven indicate that such a position favors filling of dor-

sal branches of the aorta. However, Greitz,[15] elaborating on the work of Lindblom,[25] Kjellberg,[22] and Ribbing[33] has convincingly demonstrated that such a phenomenon is not the result of a differential gravitational flow based upon a specific gravity of contrast media higher than that of blood. By studies on glass and rubber tube models, and by observations during phlebography in man, he observed that the high viscosity of contrast media favored layering rather than ready mixing with blood. He confirmed the observations of Lindblom that a laminar flow was accentuated in horizontally oriented vessels and eliminated by placing these vessels in a vertical plane. In his examples the contrast medium usually flowed beneath the layer of blood. But where vessels curved, he sometimes encountered, as did Kjellberg, a splitting of the layer of contrast medium, with one lamina following the superior wall of a vessel. With an upward flow, a direction that may be compared to a retrograde injection, he noted that a laminar flow could be produced in vertically oriented tubes. In test tubes he was able to layer Umbradil over blood, or vice versa, depending upon the order of introduction of these materials into the tubes. It is difficult to estimate how applicable these observations, made in vessels under conditions of low pressure and comparatively slow flow, are to the arterial system with its high pressure and rapid flow. Certainly, the demonstration by McDonald[27] of a turbulent flow in the rabbit aorta indicates that conditions are unfavorable for laminar flow in this animal, and that the interpretations of Hol and Skjerven may be an oversimplification of the situation. Most studies in dogs have indicated that laminar rather than turbulent flow conditions prevail. Direct studies of circulatory dynamics in the canine aorta have not been made, but McDonald and associates[17] have failed to demonstrate turbulence in vessels the size of the femoral artery. Further, McDonald,[28] using dye-coagulation injection methods, was able to show a streamline flow in the basilar artery of dogs. Smith and associates,[2,5,37] by following the localization of experimental emboli and by injecting plastic materials of different colors into the great veins, have demonstrated a stream-flow that remains discrete while passing through the right heart and pulmonary artery of dogs. In cats, observations of such streamlining of contrast media in the systemic circulation were recorded photographically by Browne and Stern[10] in the pial veins following intracarotid injections. In our own aortograms, no laminar flow was observed. However, none of our studies used high-speed sequential radiographic technics, necessary for adequate visualization of streamline flow. Inasmuch as two examples of severe spinal cord injury in man resulting from aortography in the prone position[6,44] are known to us, it is certain that the supine position is not an essential condition for this injury.

In the past, the experimental observations characterizing the contrast medium injury as a benign, reversible process have been in conflict with evidence produced by complications of cerebral angiography in man. Permanent neurological defects[1,12,31,32,40] have been observed clinically and in-

farct-like lesions have been demonstrated in postmortem studies.[12,43] Of particular value on a comparative basis is the report of Utterback and Haymaker.[43] They studied 4 fatal cases of contrast medium injury to the brain, with deaths occurring at 40 hours, 3 days, and 10 days (2 cases) following angiographic studies. In all of these cases massive infarction, focused particularly on cortical gray matter, was encountered. Necrobiotic changes in vessels, particularly arterioles, and secondary thrombus formation were a prominent feature in the 2 cases of shortest duration, and were noticeable in the other 2 cases. The close correspondence of these changes with those encountered in our experimental material indicates that the toxic manifestations in humans and animals are essentially identical. On this basis it would appear that there is no longer a need to implicate such extraneous factors as pre-existing vascular or parenchymal disease[12] or clot emboli[11] to account for the severe irreversible contrast medium injuries encountered in man.

The sharply marginated malacic lesions, closely corresponding to specific blood supply zones, are best explained as the result of the primary sweep of a toxic concentration of the contrast medium through the spinal cord circulation. This exposure is exceedingly brief, lasting no more than a minute, even when severe disturbances of flow are produced by the contrast agent.[34] Yet the fully developed lesion exceeds in severity the ischemic cord changes produced by acute aortic compression of 1 hour's duration.[24] An irreversible vascular injury, as well as widespread thrombosis, could produce such a lesion, but there is little evidence to support the latter possibility. The involvement of all tissue components argues strongly against a simple angiospastic effect.[35] The immediate convulsive reaction, which stands in sharp contrast to the delayed functional effects of hypoxia on the cord,[26] indicates a direct toxic action upon neurones, and that the injury is not entirely the result of ischemia. However, it is likely that all of the irreversible effects follow the vascular injury. For example, the early stages of the neuronal changes show a close similarity to neuronal alterations secondary to ischemia and hypoxia, both in their cytologic features and in their rate of development.[24] Whether functional alterations of vascular dynamics, thrombotic phenomena, or vasonecrotizing effects are of greater importance in the production of the disruption of circulation is difficult to determine in an essentially two-dimensional anatomical study such as this. The relative roles of these mechanisms and the precise locus of the vascular obstruction are currently under study by additional technics.

From these studies it is evident that the canine spinal cord is an ideal site for the testing of the toxic effects of contrast media upon the nervous system. In its structure and blood supply, it closely resembles the human cord. Its low anatomical position renders it especially accessible to agents injected into the aorta. Finally, the site of injury allows extended survival of the experimental animal, and an opportunity to study all developmental phases of the contrast medium lesion.

SUMMARY

The pathologic anatomy and topographic features of experimental contrast medium injury to the spinal cord, produced by aortographic procedures, have been investigated. A severe destructive effect productive of extensive myelomalacia has been encountered. These findings indicate that the previous concept of the contrast medium injury as a transitory disturbance of the blood-brain barrier is inadequate. This extension of our knowledge has been possible, because the site of injury has allowed extended survival of the experimental animals, and an opportunity to study the complete evolution of the lesion. The cord is recommended as a test site for measuring the relative toxicity of contrast media.

The histologic material was prepared under the direction of Mr. J. Phillip Pickett, and the photography was supervised by Mr. Carl Bishop.

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ENCEPHALOMALACIA SIMULATING THE CLINICAL AND RADIOLOGICAL ASPECTS OF BRAIN TUMOR

A REPORT OF 6 CASES

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> And when the time comes to make public one's score, it is done somewhat apologetically, but with the expectation that others may profit by it and with the assurance they will come to improve upon it.—HARVEY CUSHING[2]

THE differential diagnosis between cerebral vascular disease and a space-occupying lesion is a challenge, even to the experienced neurologist. The occurrence of symptoms suggesting an acute cerebrovascular disorder in patients harboring brain tumors is perhaps the greatest source of error.[6] Apoplectiform symptoms, such as occur in cases of glioblastoma multiforme, with its tendency towards intravascular thrombosis and hemorrhage, or metastatic carcinoma, or infection of the brain of embolic origin, may be the first evidence of an expanding lesion and may be indistinguishable from those of cerebral vascular disease.[15]

On the other hand, progressive symptomatology and neurological deficit may occur with generalized cerebral arteriosclerosis, or with occlusion of major intra- or extracranial vessels, such as middle cerebral or internal carotid artery. The symptoms of these vascular lesions may be indistinguishable from those of an infiltrating brain tumor.[4] Thrombosis of the internal carotid artery may simulate a mass lesion by its slowly evolving course, with headache, in at least half of the cases, preceding[5,11] or associated with progressive disability involving one half of the body.[9,17]

Even more difficult is the diagnosis in those patients whose history and clinical findings may be compatible with either cerebral vascular disease or intracranial neoplasm. Usually supplementary tests, such as cerebral angiography and/or air studies, will clarify the diagnosis. Occasionally, however, massive cerebral infarction will produce radiographic changes compatible with an expanding lesion and craniotomy is performed. The vascular etiology of the process becomes apparent only after thorough exploration and biopsy are negative for brain tumor, as well as from the further evolution of the symptoms.

The relative absence of such reports in the literature has prompted the discussion of 6 patients with encephalomalacia simulating an expanding lesion in whom craniotomy was performed.

CASE REPORTS

Case 1. E.K. (#119945), a 31-year-old female, was admitted to the Methodist Hospital on Sept. 11, 1950, with the complaint of left hemiparesis of 5 weeks' duration. About 6 weeks previously the patient had become drowsy and lethargic, sleeping 18–20 hours a day. She had some domestic difficulties, and when seen by previous examiners, her symptoms were attributed to emotional disturbances. Later, she had an episode of smelling natural gas, accompanied by a spell of moderately severe pain in the right frontal region; this was followed by generalized headache, all symptoms disappearing in approximately 18 hours. The patient was up during the night of August 9 to go to the bathroom, but on awakening the next morning, she was unable to move her left arm and had weakness of her left leg. The left hemiparesis persisted during the month prior to admission.

Examination. Blood pressure was 146/82, pulse rate 82, respiratory rate 20, and temperature 99°F. The heart was slightly enlarged to the left with the pulmonic 2nd sound greater than the aortic 2nd sound. The patient was fairly cooperative, but over-responded to any kind of stimuli. The left arm was completely paralyzed, and the left leg was markedly weak. Myotatic reflexes were increased on the left. Hoffmann and Babinski signs were present. Abdominal reflexes were absent on the left. All modalities of sensation were reduced over the left half of the body. There were poor upward and lateral gaze of the left eye, with diplopia, dullness to pin prick on the left side of the face, left supranuclear facial weakness, deviation of the tongue to the left, and the optic discs showed papilledema of 2D.

Laboratory Data. Hemogram, urinalysis, blood chemistry and serology showed no abnormalities. Spinal fluid pressure was 200 mm. of water; cell count was 10 polymorphonuclear leucocytes; protein was 96 mg. per cent. Roentgenograms of skull and chest were within normal limits. Electroencephalogram (Sept. 13, 1950) revealed a diffusely slow disorganized tracing with a discharging focus in the region of the lower end of the motor area on the right side. The findings were interpreted as compatible with the diagnosis of cerebral thrombosis, but the generalized involvement and the organization of the electric activity was considered more suggestive of a space-occupying lesion, especially glioblastoma.

Comment. A lesion in or near the internal capsule was considered with the differential diagnosis between (1) thrombosis of the middle cerebral artery, (2) encephalitic process, and (3) cerebral neoplasm. It was felt that the first possibility was most likely, but that tumor could not be excluded.

Course. A pneumoencephalogram was performed on Sept. 15, 1950. The anteroposterior projection (Fig. 1) showed dilatation of the lateral and third ventricles with displacement towards the left side; the lateral projections were not localizing. There was some difference in the appearance of the inferior horns on the two sides, but the anteroposterior projection indicated that the lesion was probably not in the temporal lobe, but above this level, appearing to be intermediate in position. A diagnosis of tumor, probably glioblastoma multiforme, was entertained.

Operation, Sept. 15, 1950. A right parietal osteoplastic flap was turned. On opening the tense dura mater near the Sylvian fissure, a 5 cm. fairly well demarcated degenerative area with hemorrhagic and necrotic changes was encountered; this area was removed by suction.

Pathological Report. The specimen consisted of several pieces of mottled pink to red tissue resembling brain in appearance with foci of hemorrhage and necrosis.

Numerous histological sections revealed areas of hemorrhage within normal brain, together with foci of encephalomalacia and glial proliferation.

Course. The patient experienced an uneventful convalescence and was discharged on the 14th postoperative day with her neurological signs unchanged.

Follow-up report from her physician on June 6, 1955, 5 years postoperatively, indicated that she was able to walk with a cane, wearing a brace on her left shoe; her left arm was quite weak. Depressive episodes occurred at intervals, and it was noted that emotional agitation increased the disability in her left arm.

FIG. 1. *Case 1.* Pneumoencephalogram showing dilatation and displacement of ventricular system towards the left, caused by an area of infarction in the right parietal lobe.

Case 2. M.G. (#83965), a 58-year-old male, was admitted to the Methodist Hospital on May 19, 1946, because of episodes of right frontal headaches of several years' duration. On April 1, 1946, while sitting, he suddenly experienced headache, and a left hemiplegia developed. This episode was diagnosed as a "stroke." Except for right hemicrania, with severe pain behind the eye and photophobia, there were no other complaints. The hemiplegia persisted with difficulty in gait, and a tendency to fall to the left.

Examination. Blood pressure was 136/80, pulse rate 60, and respiratory rate 20. The heart was moderately enlarged, with a harsh systolic murmur at the apex. There

was a left spastic hemiplegia, with increased myotatic reflexes and Babinski sign. Sensory modalities were normal. Visual acuity was generally diminished, but the optic discs were normal. The left pupil measured 6 mm., and the right pupil measured 4 mm. in diameter. Both reacted to light and in accommodation. A left lower facial weakness was apparent.

Laboratory Data. On roentgenograms of the skull the dorsum sellae appeared relatively short; this was considered to be the result of extrasellar erosion by a space-taking lesion. Cerebrospinal fluid pressure was 280 mm. of water, with 3 lymphocytes and protein 10 mg. per cent.

The clinical impression was that of a right frontal lobe lesion, vascular or neoplastic in nature. The day after admission a pneumoencephalogram was done. In the anteroposterior projection, there was displacement of the lateral and third ventricles toward the left side. Subsequent films showed little in the way of definite localizing signs. The posteroanterior projection showed no displacement of the posterior portion of the lateral ventricles. The patient was thought to have a brain tumor in the anterior two-thirds of the right hemisphere.

Operation, May 24, 1946. A large frontotemporal osteoplastic flap was turned. On opening the dura mater, exploration at a depth of 3½ cm. revealed a softened mass, dark yellow in appearance, extending from the posterior frontal lobe down to the basal ganglia and temporal lobe. No signs of hemorrhage were seen. Several biopsies were taken and the area of softening was removed by suction.

Pathological Report. Numerous microscopic sections revealed areas of necrosis surrounded by newly formed capillaries and gitter cells. There were foci of nerve fiber degeneration. No neoplastic cells were seen. The findings were considered compatible with the diagnosis of encephalomalacia.

Course. The patient was discharged on the 15th postoperative day with his hemiplegia steadily clearing.

On June 6, 1955, 9 years postoperatively, the patient appeared alert and was up most of the time, experiencing a few occasional headaches, especially when nervous. He could walk with assistance.

Case 3. C.C. (#6496), a 64-year-old male, was first seen as an outpatient on Aug. 6, 1951, because of difficulty in his speech. There had been "slowly progressive speech impairment" for about 1 month, consisting in a loss of words, accompanied by slight weakness of the right leg. He gave a history of unconsciousness for 3 days following a head injury about 20 years before. On examination, he was alert and cooperative. The pupils were equal, regular and reacted to light and in accommodation. The myotatic reflexes were within normal limits. Abdominal reflexes were absent bilaterally. A moderate degree of motor aphasia was present. With the clinical impression of occlusion of the middle cerebral artery (probably on an arteriosclerotic basis), he was put on papaverine and nicotinic acid. Fifteen days later (Aug. 21, 1951), he was admitted to St. Joseph's Hospital because of progression of weakness in the right extremities and further speech difficulty.

Examination. Blood pressure was 120/80, pulse rate 64, and respiratory rate 20. There was a sensory and motor aphasia of mild degree. Objective weakness of the right extremities with increased myotatic reflexes was noted. Bilateral papilledema and a right supranuclear facial weakness were present.

Laboratory Data. Cerebrospinal fluid pressure was 210 mm. of water, with 1

lymphocyte, protein 111 mg. per cent, and negative Kolmer. Roentgenograms of the chest were negative. Films of the skull (Fig. 2) revealed definite shift of the calcified pineal body to the right of the sagittal plane. Pneumoencephalography on Aug. 25, 1951 revealed, in the anteroposterior projection (Fig. 3A), a considerable distortion of the ventricular pattern with displacement towards the right. In the lateral projection (Fig. 3B), the anterior horn was cut off with extreme downward-bending of the body of the left lateral ventricle, suggesting a large tumor in the left frontoparietal lobes.

Operation, Aug, 25, 1951. A large left osteoplastic flap was turned. Exploration

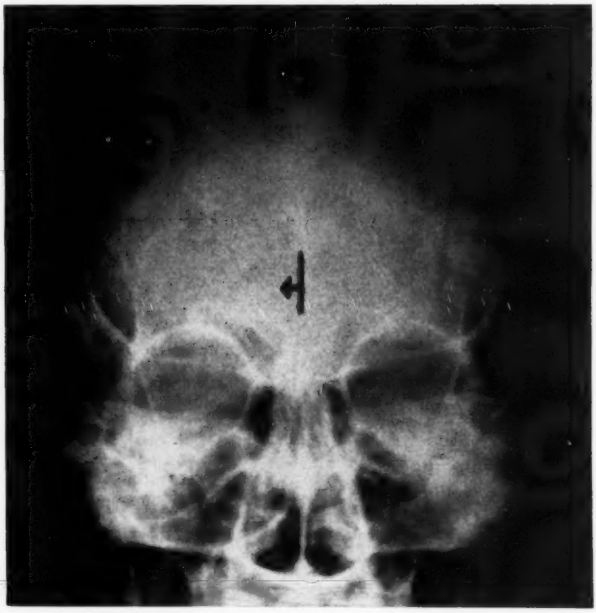

FIG. 2. *Case 3.* Displacement of pineal gland to the right by an infarction in the left hemisphere.

of the posterior part of the frontal lobe and anterior part of the parietal lobe failed to reveal the presence of a tumor. At a depth of about 2 cm. in the parietal lobe, yellowish, soft tissue was encountered and aspirated. Frozen sections revealed an area of infarction with multiple hemorrhages.

Pathological Report. Microscopic sections revealed brain tissue with evidence of infarct and multiple areas of petechial hemorrhage. The findings suggested encephalomalacia and hemorrhage.

Course. The patient died the day following surgery. Permission for autopsy was refused.

Case 4. C.H. (#7879), a 69-year-old male, was admitted to St. Joseph's Hospital on Oct. 5, 1953, because of "progressive left hemiparesis," which had developed in the last 5 weeks. During this time, he had been complaining of dizziness, loss of mem-

ory, and irritability. For the last several days he had had right supraorbital headaches, and frequent episodes of vomiting and drowsiness. There was a history of fall from a chair about 2 months prior to admission, following which there was some weakness in the left leg and arm.

Examination. The patient appeared fairly cooperative, but was slow in following commands. No voluntary motion was present in the left extremities. Myotatic reflexes were increased bilaterally, with a Babinski sign on the left. The pupils reacted to light and in accommodation. There was papilledema of 2–3 D. A left supranuclear facial weakness was noted.

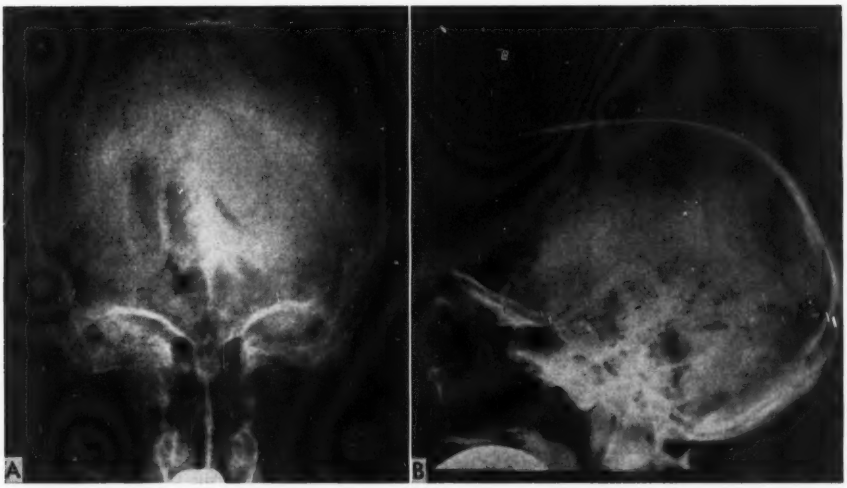

FIG. 3. *Case 3.* (A) Pneumoencephalogram showing massive shift of ventricular system in anteroposterior view and (B) distortion of left lateral ventricle in lateral view. Encephalomalacia, left hemisphere, simulating left frontoparietal tumor.

Laboratory Data. Roentgenograms of the chest and skull were noncontributory. Ventricular fluid contained 4 lymphocytes and 66 mg. per cent protein.

Because of the history of a fall, a subdural or subcortical hematoma was considered, but the most likely diagnosis appeared to be brain tumor.

Course. During the 2 days following admission, his condition became progressively worse. He was drowsier, had more frequent headaches and vomiting, and became almost completely hemiplegic. Difficulty in swallowing and hiccoughing developed.

Ventriculography on Oct. 10, 1953 revealed marked displacement of the lateral and third ventricles to the left, with some decrease in size of the right lateral ventricle. These findings were thought to indicate a large neoplastic growth in the right frontotemporal area (Fig. 4).

Operation, Oct. 10, 1953. A large right frontotemporoparietal flap was turned. On opening the dura mater, the temporofrontal region was found to be yellowish in color, and the gyri in this area were flattened. Softened brain tissue was encountered below the surface of this area; further exploration failed to reveal any tumor. A

small, 1.5 cm. cyst was found, and biopsies from this and adjacent areas were taken. A diagnosis of encephalomalacia, secondary to cerebral thrombosis, was made. The wound was then closed without removal of the infarcted area.

Pathological Report. Microscopic sections revealed focal areas of fairly recent hemorrhage. There was also some increase in glial elements. Some of the ganglion cells of the cortex showed early pyknosis and neuronophagia. In one of the specimens, a focus of calcification was found. The findings were consistent with the periph-

FIG. 4. *Case 4.* Ventriculogram showing displacement and distortion of ventricular system caused by a large area of infarction in right frontotemporal region.

eral zone of an area of encephalomalacia. The calcification was considered possibly to represent a late stage of a minute previous infarct. No evidence of neoplasm was found.

Course. The patient remained in coma following craniotomy, and died within the next 7 hours. Permission for autopsy was refused.

Case 5. H.G.S. (#35041), a 44-year-old male, was admitted to the Methodist Hospital on Dec. 25, 1953, because of right hemiparesis. Ten days before, he had noticed stiffness of the right leg with loss of feeling. Later a sensation of stiffness developed in his right hand, and he did not write as well as formerly. He experienced

occasional headache during this period, and had an episode of transient mental confusion, of which he was aware.

Examination. Blood pressure was 140/80, pulse rate 80, respiratory rate 18, and temperature 99°F. Positive neurological findings were: loss of balance and falling to the right on Romberg; right pupil larger than the left and not reactive to light; and hypalgesia on the right side of the body. No speech difficulty was noticed at that time.

Laboratory Data. Roentgenograms of chest and skull were normal. Cerebrospinal fluid pressure was 220 mm. of water, with 3 lymphocytes, 1 polymorphonuclear leucocyte and 52 mg. protein. Electroencephalogram on Dec. 28, 1953 showed depression of normal alpha rhythm in the left hemisphere, very slow, low voltage activity focal in the left occipital region, and a focus of irregular 3–5 c./sec. waves in the left inferior central region. These findings suggested that a vascular lesion be strongly considered. A tentative diagnosis of thrombosis of the left middle cerebral artery was made.

Course. Within the next few days, the patient showed progression of the right hemiparesis to nearly complete hemiplegia. On Jan. 1, 1954, a right homonymous hemianopsia was noted. The right pupil remained larger than the left, and did not react to light. A right thalamic type of facial paresis appeared. Severe involvement of all sensory modalities on the right side was observed. The patient was euphoric and confused.

In view of the progression of the symptomatology, pneumoencephalography was performed on Jan. 4, 1954. After injection of 30 cc. of air, a scout film taken in the upright position showed no filling of the ventricles. Accordingly, a left carotid angiogram was then performed, which showed in the lateral projection (Fig. 5, right) considerable elevation of the second portion of the middle cerebral artery. In the anteroposterior projection (Fig. 5, left) the anterior cerebral artery was slightly displaced across the midline towards the right, with no elevation of the first portion of the middle cerebral artery. These findings were considered to be caused by a space-occupying mass in the middle portion of the temporal lobe. Because of respiratory difficulty, the patient was taken immediately to the operating room with the preoperative diagnosis of left temporal lobe tumor, or area of softening.

Operation, Jan. 4, 1954. A left temporal flap was turned. After opening a somewhat tense dura mater, the middle and posterior part of the temporal lobe were needled deeply and about 10 cc. of yellow, thick, necrotic, bloody material was aspirated. The lower temporal area was removed to relieve the tremendous intracranial pressure, the dura mater was left open, and the scalp was closed in layers.

Pathological Report. Microscopic sections of the biopsy specimen revealed blood clot, fibrin and extremely necrotic tissue. In one area there was a small artery revealing recent thrombotic occlusion. Where better preservation of brain tissue was seen, there was considerable infiltration of polymorphonuclear leucocytes and macrophages, together with proliferation of glial elements. Some parts of the section revealed marked endothelial proliferation of blood vessels. In none of the sections could neoplastic tissue be recognized.

Course. The patient remained in deep coma following surgery, and died on the 3rd postoperative day.

Necropsy. There was no evidence of occlusion of the vertebral or carotid arteries, as they entered the cranial cavity. The brain weighed 1570 gm. The vascular circle

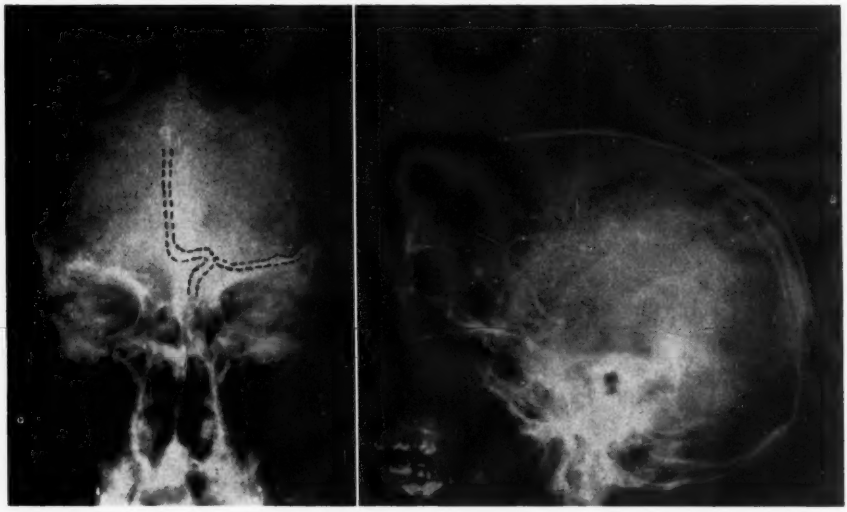

FIG. 5. *Case 5.* Left carotid angiogram showing displacement of anterior cerebral artery across the midline in anteroposterior view and marked elevation of the Sylvian group in lateral view, caused by softening of temporal lobe, basal ganglia and thalamus, simulating tumor of temporal lobe.

at the base of the brain was markedly distorted because of softening and infarction. Coronal section at level of the optic chiasma revealed marked distortion, particularly on the left, with a ventricular shift to the right. There was a well delineated area of discoloration with softening involving most of the left temporal lobe, and the entire region of the basal ganglia and thalamus. This part of the brain was extremely friable and "fell out" of the remaining portion of the brain when cut. Sections through the cerebral hemispheres, posteriorly, revealed extension of the process to the occipital poles. In the occipital region, on the left, there was evident cortical necrosis, measuring 4 cm. in its greatest dimension. Sections anteriorly from the region of the optic chiasma revealed marked perineuronal edema and encephalomalacia. Extensive areas of infarction and hemorrhage were also present. In the sections showing hemorrhage there were large numbers of macrophages.

Case 6. G.F.S. (#53534), a 61-year-old male, was admitted to the Methodist Hospital on Nov. 17, 1954. One year previously he had been hospitalized because of an episode of jerking sensation in the throat and difficulty in swallowing. He subsequently did well until 1 month prior to admission when he had sudden pain in the left leg, followed by numbness and weakness. While being carried to the hospital, he became confused and was unaware of what was happening. Shortly thereafter, he was able to carry on a normal conversation, and his sensorium appeared clear. There was a history of jerking in the left arm and leg during this second hospitalization. After a week he was able to resume normal activities. Two weeks later the left arm and leg again became weak, and there was another episode of memory lapse. At the end of his day's work, he was unable to find his car parked in a place usually familiar to him. He was hospitalized for the third time, and had two lumbar punc-

tures, both reported normal as to pressure and cerebrospinal fluid constituents. There was, in addition, a history of frontal headaches in the month prior to the transfer to the neurosurgical service.

Examination. Blood pressure was 110/70, pulse rate 65, and respiratory rate 18. Patient was alert and cooperative. There was definite weakness of the left extremities. Myotatic reflexes were hyperactive bilaterally. The Hoffmann sign was positive on the left. There was loss of position sense and of stereognosis on the left. The cranial nerves were normal.

Laboratory Data. Roentgenograms of the chest showed generalized pulmonary emphysema without evidence of significant intrathoracic abnormality. Films of the skull (Fig. 6, above, right) showed significant displacement of the pineal gland towards the left. Electroencephalogram (Nov. 18, 1954) revealed a very active discharging slow wave focus in the right parietotemporal region with wide areal reference in all right leads. These findings were considered nondiagnostic, but the possibility of a neoplasm was considered.

The clinical impression was that of thrombosis of the right middle cerebral artery or cerebrovascular insufficiency[1] in the right hemisphere, with a parietal lobe tumor to be ruled out.

Course. The day following electroencephalography, the patient had an episode of headache and vomiting and appeared confused and drowsy. This episode was attributed to acute increase of intracranial pressure secondary to brain tumor, and on Nov. 21, 1954, ventriculography was done. This revealed in the anteroposterior projection (Fig. 6, above, left) dilatation of the left lateral and third ventricles with displacement of the entire ventricular system towards the left. This suggested a space-occupying lesion located in the inferior portion of the right parietal lobe and superior portion of the right temporal lobe. The preoperative diagnosis was tumor of the right temporoparietal lobes.

Operation, Nov. 21, 1954. A right parietotemporal flap was turned. The dura mater appeared extremely tense, but was opened without difficulty after escape of fluid from the left lateral ventricle. On the surface of the brain in the parietal region a yellow, avascular area was found. The cortex was incised in this region and soft, mushy brain was aspirated through the incision. The area surrounding the above-described infarction was also soft, mushy and yellowish in color. No evidence of tumor could be found by needle exploration. The wound was then closed without removal of the infarcted area.

Pathological Report. Microscopic sections of the biopsied material revealed brain tissue with evidence of demyelinization, pseudocystic changes and atrophy. The small blood vessels appeared intact, but their walls were markedly hyalinized. Considerable necrosis and a few small focal hemorrhages were seen. The findings suggested encephalomalacia.

Course. The patient remained in coma following operation, and died on the 2nd postoperative day.

Necropsy. The fixed brain weighed 1550 gm. The hemispheres were approximately symmetrical, but there was transtentorial herniation of the right uncus. There was minimal patchy sclerosis of the vertebral and basilar arteries; the remainder of the circle of Willis was normal. The major portion of the middle cerebral arteries revealed patchy arteriosclerosis, but no evidence of hemorrhage was seen in the surrounding tissue. Section at the level of the optic chiasma revealed a marked increase of the mass of the white matter on the right with herniation of the cingulate gyrus

under the falx to the left, and marked displacement of the ventricular system to the left with compression of the lumen of the left lateral ventricle (Fig. 6, below). An operative defect was evident in the right parietal lobe extending from the surface to the corona radiata.

Microscopic examination in the region of the operative site revealed areas of hemorrhage, acute and subacute inflammatory reaction, and occasional macrophages. Throughout many of the sections were small focal areas of hemorrhage and

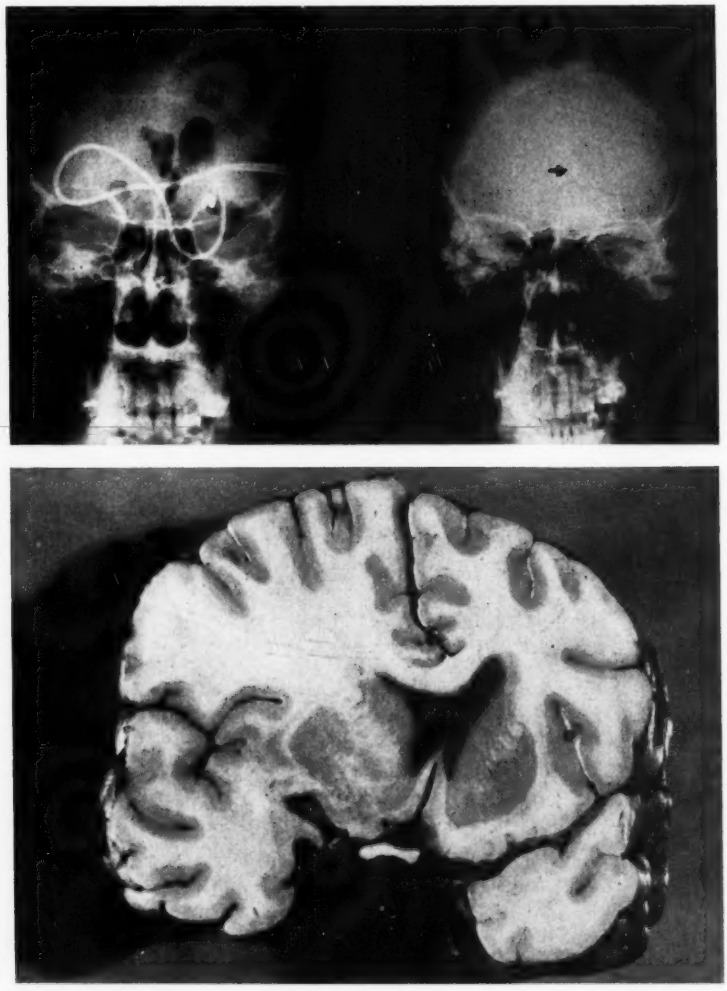

FIG. 6. *Case 6.* Massive infarction of right cerebral hemisphere with edema (*below*), causing shift of the pineal gland (*above, right*), and displacement of the ventricular system (*above, left*), simulating a tumor in right temporoparietal region.

a slight degree of endothelial proliferation. The smaller blood vessels revealed well marked arteriosclerotic changes with hyalinization and/or hemorrhagic extravasation. Sections of the cerebrovascular tree revealed no thrombi nor emboli.

COMMENT

In this small series, data concerning age must necessarily be inconclusive: the ages were respectively 31, 44, 58, 61, 64 and 69 years. The 2 survivors in this group were 31 and 58 years of age.

The clinical symptomatology and signs may be classified into three categories: (1) focal neurological signs, (2) seizure phenomena and (3) signs of increased intracranial pressure. Thus, focal neurological signs, such as hemiparesis or hemiplegia, hemisensory defect, and speech impairment (aphasia) were frequently present. Seizure phenomena were also noted, such as uncinate fits, focal convulsions and psychomotor spells. Signs and symptoms of increased intracranial pressure were present in all cases at some time during their course; these included headache, nausea, vomiting, drowsiness, papilledema and increased cerebrospinal fluid pressure on lumbar puncture. It is of interest in the evolution of the symptomatology and neurological signs, that evidence of increased intracranial pressure was noted from 2 to 7 weeks after the onset of symptoms. In 3 cases there was evidence of progression of the findings at the time of admission, with rapid deterioration in 2 and slower progression in the other. In some cases, the focal neurological signs were preceded by seizure phenomena and/or changes in sensorium.

The clinical impression, when the patients were first seen, was that of thrombosis of the middle cerebral artery in 4 instances (Cases 1, 3, 5 and 6); intracerebral hemorrhage (Case 2), and/or subdural hematoma (Case 4); the latter 2 because of a history of head injury.

An electroencephalogram was obtained in only 3 cases. In 2 cases, there was a slow wave focus suggesting a brain tumor; in the third case, the findings were considered strongly suggestive of a vascular lesion. This emphasized the difficulty of differential diagnosis between vascular lesion and infiltrative glioma on the basis of electroencephalography alone. According to Strauss and Greenstein,[20] focal delta activity would favor neoplasm over thrombosis in a ratio of 8:1; but they do not believe that there are typical patterns specific for either. Murphy and Duggins,[14] comparing electroencephalographic records of glioma and cerebral infarction, found "inconstant" irregular slow discharges, in the region of the lesion, in 86 per cent of tumor patients, whereas irregular slow waves of "constant" appearance were seen in 70 per cent of the patients with thrombosis. Further information might be obtained by serial electroencephalographic records, when possible, in cases in which such a problem in differential diagnosis arises.

Skillicorn and Aird,[18] during electroencephalographic recordings, have performed digital compression of each carotid artery in turn, below the sinus, and in 15 (25 per cent) of 60 unselected patients, found marked electroencephalographic changes on unilateral compression of the common carotid

artery. Eleven of these 15 patients had a diagnosis of "cerebrovascular disease." The electroencephalographic response to unilateral compression of the common carotid artery may serve to indicate the presence of cerebrovascular insufficiency.[1,18]

Roentgenograms of the skull were not obtained in 1 case. In 3 others, in which the pineal gland was not visualized, the films were considered normal, except in 1 instance in which there was extrasellar erosion. In the remaining 2 cases, there was a measurable and significative pineal shift away from the infarcted area. Occasional cases have been reported of displacement of the pineal gland caused by infarction secondary to thrombosis.[5,11,12,13]

Air studies were done in all cases in the present series. The common feature was ventricular displacement toward the side opposite the infarction, except in 1 case in which there was no air filling the ventricular system. A pronounced shift of the lateral and third ventricles, caused by softening of one hemisphere, has been observed in a case of traumatic carotid artery thrombosis.[16] Elvidge and Werner[5] reported 3 cases of displacement of the ventricular system caused by ipsilateral cerebral edema at 3, 6 and 12 days following the onset of signs of thrombosis. In the case reported by King,[12] there was evidence of thrombosis of the internal carotid artery; subsequent ventriculogram showed marked ventricular shift away from the side of thrombosis. An area of infarction was considered, but the clinical course made the diagnosis of cerebral neoplasm more likely. Both craniotomy and necropsy revealed massive softening of almost one entire hemisphere.

Because of the massive and diffuse nature of the infarcted area, usually in the distribution of the middle cerebral artery, accurate localization from the ventriculographic appearance was extremely difficult. In only 2 cases was the lesion apparently pin-pointed satisfactorily; in the remainder, a less accurate interpretation was made as to the areas involved.

Only one angiogram was done in this series. This revealed an apparent posterior or middle temporal lobe lesion; there was no evidence of vascular occlusion. Cerebral infarction, without visible obstruction, has been recognized by several authors,[7,10,19] and explained by a variety of mechanisms. It should be pointed out, as well, that necropsies are often incomplete, and the carotid arteries in the neck are not systematically studied. This would suggest that a large number of cases of carotid artery thrombosis may be unrecognized even at necropsy.[7,10]

It is not the aim of this paper to discuss the causes of cerebral infarction. Of the cases of encephalomalacia found in the literature, in all instances in which there was displacement of the pineal gland and ventricular system, angiograms revealed thrombosis of the carotid artery or one of its branches.[5,11,12] The increasing frequency with which occlusion of the carotid artery recently has been reported[3,8,17] indicates that thrombosis is much commoner than has been heretofore believed, and may very well be the most frequent cause of cerebral infarction. In the present series, internal carotid artery thrombosis was not satisfactorily ruled out since arteriography was

done in only 1 case. In that case, and in the other 2 in which necropsy failed to reveal evidence of occlusion of the vertebral and carotid arteries and their branches, ischemic rather than thrombotic infarction appeared to be the cause of the encephalomalacia. In the remainder of the cases, the cause was unrecognized.

For this reason, the use of cerebral angiography, if necessary, combined with air studies, is suggested in any patient whose history and clinical picture suggest a vascular lesion. When air studies are indicated and performed, the evaluation in the light of the clinical picture may aid in their interpretation. The anteroposterior projection often indicates a massive displacement of the ventricular system, but with the lateral projection, at times, not aiding in localization.

If surgery is considered and carried out, and if exploration is negative for brain tumor, with frozen sections indicating cerebral infarction (encephalomalacia), removal of the necrotic area seems to be of benefit. In 3 cases in which repeated needling failed to reveal the suspected tumor, and only biopsy was performed, there was a fatal outcome. Two of the other 3 patients, in whom adequate removal of the necrotic area was carried out, are still living at 5 and 9 years respectively since surgery. Both of these patients show no signs of recurrence or of progression of their previous disability. It seems reasonable to believe that the infarction, with surrounding edema, acts as a mass lesion exercising a compressive action on the neighboring structures. The common surgical and pathological finding in such cases has been the association of encephalomalacia and hemorrhage, with marked cerebral swelling (see Fig. 6) and signs of increased intracranial pressure. Removal of this abnormal area may give relief of pressure, perhaps followed by improvement of symptomatology.

SUMMARY

In some cases of cerebrovascular disease with encephalomalacia there may be clinical symptoms and signs simulating those of an expanding intracranial lesion, requiring the exclusion of a diagnosis of brain tumor.

Diagnostic studies, including electroencephalograms, roentgenograms of the skull, air studies, and angiography, may support this clinical impression, indicating a mass-lesion.

Six cases are reported of patients with focal signs and increased intracranial pressure in which operation failed to reveal evidence of cerebral neoplasm, but in which the diagnosis of infarction and encephalomalacia was established.

A discussion of the clinical, radiological, operative and pathological aspects of these cases is presented.

Radical removal of the infarcted area was performed in 3 cases, and appears to offer more satisfactory prognosis than does partial removal or simple biopsy.

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THE FATE OF PATIENTS WHO HAVE CEREBRAL ARTERIOVENOUS ANOMALIES WITHOUT DEFINITIVE SURGICAL TREATMENTS

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INDICATIONS for operation in any given condition must be drawn from the balance remaining between the risks attending surgery, not only to life but to function, on the one hand, as opposed to the risk to life and to function if surgery is denied. This probably is no more true than in the case of arteriovenous anomalies of the brain, in which the operative mortality rate is at least 11.7 per cent,[6] and in which the risk to function is real because of the fact that these lesions so frequently lie in the sylvian and rolandic fissures.

The literature on the fate of these patients for whom no definitive surgical procedure has been carried out is scanty and conflicting. We have therefore reviewed our series of cases from the standpoint of natural history and course of the pathologic process.

Between 1930 and 1954, 51 patients with proved cerebral arteriovenous anomaly have been studied at the Mayo Clinic. The presence of the lesion was verified either by surgical exploration or by cerebral angiography. We rejected, for purposes of this review, a considerable number of cases in which there was strong reason to suspect that an arteriovenous anomaly was present, but in which adequate verification was not obtained. Of this group of 51 patients, 23 received no definitive treatment. The surviving patients of this group have either been re-examined during 1954 or have answered questionnaires regarding their present status and their histories during the interval. In those cases in which the patients' answers by letter were not deemed satisfactory, the attending physician was consulted and he supplied the necessary information.

The analysis of these cases will be considered from the standpoint of the usual symptoms presented by these patients.

INTRACRANIAL BLEEDING

Olivecrona wrote that "in the end, probably most, if not all patients die of hemorrhage or are completely incapacitated." He also wrote that almost

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half of his patients had a history of one or more hemorrhages with hemiplegia, which was often transient, although some degree of motor or speech defects usually remained. Dandy[2] wrote that death resulted from cerebral hemorrhages in 40 per cent of these cases. In Mackenzie's[4] series of 50 patients, 15 presented a history of intracranial hemorrhage. Bassett[1] reported on 18 patients, 11 of whom had subarachnoid hemorrhages, some of them with recurrent bleeding, but he thought that the hemorrhages rarely were fatal and that they were not so devastating as those caused by rupture of an aneurysm. Gould and associates[3] encountered subarachnoid bleeding in 15, and intracerebral bleeding in 9, of 41 patients (an incidence of intracranial bleeding of 56 per cent). The mortality rate from hemorrhage was 20 per cent of the entire series.

In our series of 23 patients, 9 (39.1 per cent) have had intracranial bleeding. Seven of these patients have had subarachnoid hemorrhages and 2 had what appeared historically and clinically to have been intracerebral hematomas.

Of the 7 patients who have had subarachnoid bleeding, 2 have died, both in their first attack; one of these patients (Case 13) had had temporal-lobe attacks for 2 years, while the other (Case 19) had had jacksonian convulsions on the average of two times a year for 22 years. The mortality rate from intracranial bleeding in this group of 23 patients is thus 8.7 per cent.

One patient (Case 4) has had three attacks of subarachnoid bleeding, the first one occurring as the first symptom of her disorder in 1932. The last episode of bleeding occurred in 1942. None of these attacks produced crippling symptoms, and at the time of this report she was in good physical and mental health. In 2 patients some degree of partial hemiparesis developed with their attacks of subarachnoid bleeding. One of these (Case 23) 5 years later had only slight hemiparesis and was working full time, as this report was written. The other (Case 22) became moderately hemiparetic at the time of his subarachnoid hemorrhage, and 5 years later wrote that his hemiparesis was no worse and that he was in good health, except for this disability. The other 2 living patients (Cases 5 and 20) both sustained the bleeding in 1941, and had not had subsequent hemorrhages as this was written. Both were working full time and were in good health, except for occasional episodes of convulsions.

Thus, of the 5 patients who survived subarachnoid hemorrhage, 3 have no residual paralytic or speech defects and 2 have some degree of residual hemiparesis. Examination of Table 1, in which are depicted the locations and approximate sizes of these lesions, suggests that in each instance extirpation of the lesion very probably would have been accompanied by rather marked hemiparesis, with speech defects, in addition, in 2 instances (Cases 4, 5, 20, 22 and 23).

Two patients, as judged on the basis of examination and findings, had intracerebral hemorrhages. One of these patients (Case 29) had had headaches for 21 years before examination in 1941. At that time she had impairment of memory and bilaterally choked optic disks. She was last examined

in November, 1954, at which time she was invalided because of hypertension, pain in the legs and marked obesity. There was no paralysis. Loss of memory was marked. Extirpation of the lesion undoubtedly would have produced some degree of hemiparesis.

The other patient who in all likelihood sustained an intracerebral hemorrhage (Case 2) had had headaches for a year before she was examined. She returned in 1954 with right-sided weakness and severe headaches, with clear cerebrospinal fluid. The hemiparesis cleared gradually. Repeated carotid arteriography demonstrated a shift of the anterior cerebral artery to the right side. This arteriogram also demonstrated an unusual circumstance in that many of the tangled arteries and venous channels were obliterated. She received deep roentgen therapy during the interim between the two arteriograms, but it is doubtful that this treatment resulted in obliteration of two-thirds or more of the abnormal vascular channels in her lesion.

The mortality rate in our series in those cases in which intracranial bleeding occurred was 22.2 per cent; this figure includes one case in which the episode of bleeding was considered to have been a possibility by the attending home physician, but necropsy was not performed.

CONVULSIONS

Convulsive disorder was the main complaint, or one of the main presenting complaints, of 15 of these 23 patients. In 6 of these patients (Cases 4, 5, 11, 20, 35 and 41) the attacks were generalized; in 6 (Cases 19, 26, 28, 30, 44 and 51) they were jacksonian; and in 3 (Cases 1, 13 and 43) they were temporal-lobe attacks.

The condition of all 6 patients with generalized convulsions was satisfactorily controlled by medication, and operation would not be considered for the convulsive disorder alone. Two of these patients had not had convulsions for many years at the time of this report. One of these (Case 4) had convulsions from 1933 to 1936, but had had none since. The other patient (Case 11) had generalized convulsions from 1934 to 1936, preceded by transient attacks of numbness for a year. He had not had any convulsive disorders since 1939.

The patients with jacksonian attacks fared as well as those with generalized convulsions. One patient (Case 19) had two attacks a year, an occurrence that continued until his death 5 years later from subarachnoid bleeding. In another patient (Case 26) jacksonian attacks occurred two times a year for 4 years, at which time he died from a cause unknown to us. The condition of one patient who had occasional focal attacks for 25 years was unchanged. Another patient had focal attacks once a month for 6 years with her menstrual period. Two patients were better. One of these (Case 28) had focal attacks every 2 months for a year, but had had no attacks since 1942, to the time of this writing. Another patient (Case 51) had had minor jacksonian episodes for 9 years, followed by major attacks with loss of consciousness for 2 years, averaging one every 6 months. For the 2 years, at the time of this report, he had had only occasional minor attacks.

Two patients with temporal-lobe attacks died (Cases 1 and 13), one from carcinoma of the lung and the other from subarachnoid bleeding. In these, the attacks were fairly frequent. In Table 1, which indicates the location of the lesion, it is evident that serious neurologic and speech deficits would have attended surgical removal of these lesions. The condition of the third patient with temporal-lobe attacks was well controlled by means of medication. Her lesion is on the medial aspect of the parietal lobe, and is relatively inaccessible.

Thus, it would appear from this survey that convulsions caused by these lesions usually are well controlled by medication, and that in a few instances the attacks disappear, or, at least, long periods of freedom from attacks intervene.

PROGRESSIVE NEUROLOGIC DEFECT

Five patients (Cases 22, 23, 27, 30 and 49) at the time of their initial examination presented varying degrees of hemiparesis. In 3 patients, the hemiparesis developed gradually and progressed over a period of years. One patient, who had had mild hemiparesis which developed over a period of 2 months, died after pneumoencephalography. The cerebrospinal fluid just before death was clear. Of the 2 in this group alive at the time of this report, one was invalided in a county home, and the other was not incapacitated.

In 2 patients (Cases 22 and 23) hemiparesis developed at the time of subarachnoid hemorrhage; it persisted in a slowly progressive form in one patient, while the other patient is no worse. Both patients sustained bleeding in 1950, and their condition was followed to January, 1955.

Table 1, in which the approximate size and location of the lesions are depicted, indicates that surgical extirpation would have resulted in hemiparesis in each of these cases.

HEADACHES

Five of these patients (Cases 2, 22, 23, 39 and 44) had severe headaches as one of their main presenting complaints. Three of them continued to have headaches as before, at the time of this report. However, in 2 patients headaches ceased; in one for $3\frac{1}{2}$ years, and in the other for 5 years, as this was written. These patients had had severe headaches for 7 and 20 years, respectively.

MENTAL RETARDATION

Olivecrona[6] wrote that mental deterioration is a common feature of inveterate lesions, and he believed that this observation strengthens the argument for removal of the lesion. Norlén[5] also wrote that mental deterioration is common among these patients and is often profound. Gould *et al.*[3] observed this feature in 7 of 41 patients (17.1 per cent). However, Mackenzie[4] found mental deterioration to be rare and detected no instance of severe retardation in his 50 patients. Only one patient (Case 39) in our series exhibited signs of mental deterioration. This patient complained of some loss of memory during the 2 years prior to his admission in 1941. On examination, he

TABLE 1

Salient data concerning 23 patients with cerebral arteriovenous anomalies

Case	Age*	Symptoms, duration years	Main presenting symptom	Lesion, location	Sub. hem.†	I.C. hem.‡	Condition*
1	40	5	Temporal-lobe attacks		0	0	Temporal-lobe attacks continued as before. Died Jan. 1955. Carcinoma of lung
2	51	4	Intermittent headaches		0	1x	Intermittent headaches as before. Not incapacitated
4	44	20	Subarachnoid hemorrhage (1932). Occasional convulsions		3x	0	Last subarachnoid hemorrhage 1942. "Getting along fine." "No convulsions in years"
5	31	11	Subarachnoid hemorrhage (1941). Generalized convulsions (6)		1x	0	Generalized convulsions 3 times a year. Working full time
11	41	22	Episodic transitory numbness, left hand. Generalized convulsions (8); none since 1939		0	0	No convulsions since 1939. Occasional numbness, left side. Working. Slight left hemiparesis
13	31	2	Temporal-lobe attacks every 3 weeks		1		Died in first subarachnoid hemorrhage 2 years after onset of symptoms
19	62	22	Jacksonian convulsions each year		1	0	Convulsions continued 2 times a year. Died in first subarachnoid hemorrhage 1947
20	61	14	Subarachnoid hemorrhage (1941). Generalized convulsions and petit mal each month		1	0	Occasional temporal-lobe attack. Not incapacitated
22	26	10	Headaches. Subarachnoid hemorrhage (June 1950). Hemiparesis		1	0	"Semiparetic." No headaches past 3½ years. "Enjoying fairly good health"
23	42	5	Headaches each month since 1930. Subarachnoid hemorrhage (Feb. 1950); slight hemiparesis		1	0	Slight weakness right side. Working full time
26	39	9	Transient numbness, left hand. Jacksonian convulsions each 2 months		0	0	Convulsions each 2 months. Died Cause?
27	53	26	Progressive hemiparesis		0	0	Hemiparetic, otherwise no complaints Invalid
28	28	16	Jacksonian convulsions		0	0	No convulsions since 1942. Working full time
30	28	23	Progressive hemiparesis; jacksonian convulsions		0	0	Hemiparetic, occasional convulsion. Not incapacitated
35	33	8	Generalized convulsions each 2 months		0	0	Convulsive disorder satisfactorily controlled by medication
39	54	33	Headaches		0	Probable	Headaches each month, memory loss. Mental deterioration
40	41	7	Episodic tinnitus		0	0	Tinnitus as before. Not incapacitating. No worse
41	51	3	"Temporal-lobe attacks"		0	0	No convulsions past 2 years. Taking anticonvulsant medication

* At time of this report.
† Subarachnoid hemorrhage.
‡ Intracranial hemorrhage.

Table Continued

Case	Age*	Symptoms, duration years	Main presenting symptom	Lesion, location	Sub. hem.†	I.C. hem.†	Condition*
43	61	3	Generalized convulsions, 2 episodes		0	0	Occasional attacks of dizziness. Infrequent convulsions on medication
44	36	8	Jacksonian convulsions and headaches each month		0	0	Jacksonian attacks and headache with menses. Not incapacitated
49	36	1/4	Progressive hemiparesis		0	0	Died after pneumoencephalography. Spinal fluid clear. No necropsy
50	37	2	Transient aphasia, dizziness, tinnitus each 6 months		0	0	Attacks as before
51	37	13	Jacksonian convulsions with unconsciousness each 6 months for 2 years		0	0	Minor attacks of "shaking" in right arm each month. Not incapacitated

* At time of this report.
† Subarachnoid hemorrhage.
‡ Intracranial hemorrhage.

was found to have choked optic disks, and a blood pressure of 170 systolic and 110 diastolic. He was seen again in 1954, at which time his blood pressure was 300 systolic. Loss of memory had increased, and there were other evidences of progressive mental deterioration.

SUMMARY

The fate of 23 patients who had arteriovenous anomalies and for whom no definitive neurosurgical procedures were carried out has been reviewed. Because the series is small, the mortality rate and other data may not be entirely valid. However, the condition of some of these patients has been followed since the 1930's and provides some indication of the fate of the patients.

The group mortality rate from intracranial bleeding was 8.7 per cent. Only one patient with intracranial bleeding was invalided because of this complication. Two other patients had residual hemiparesis, but continued to work. When it is considered that the mortality rate of radical extirpation of such lesions is at least 11.7 per cent, that excision cannot always be complete, and that because of the location of these lesions residual neurologic defects have to be expected in most cases, this study suggests that intracranial bleeding in itself is a dubious indication for operation.

Analysis of the convulsive disorders presented by these patients indicates that in the majority of patients such afflictions can be satisfactorily controlled medically, and that in a significant number of cases convulsions disappear. When, again, the risk of surgery and the fact that surgical extirpation is no guarantee that convulsions will disappear are considered, it is the opinion of the authors that on the basis of the convulsive disorder alone, operation is not justified for many of these patients.

Progressive hemiparesis developed in 13 per cent of patients in this series. This figure corresponds to the mortality rate of surgical extirpation; in

most cases the neurologic defect produced by surgery would be almost as profound as that obtaining had the lesion not been treated surgically.

Mental deterioration was present in one of these 23 patients. Our experience in this regard is similar to that of Mackenzie, and is contrary to that of Olivecrona and Norlén.

It is our opinion, derived from this review, that headache alone rarely constitutes an indication for surgical intervention.

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POSITIVE CONTRAST VENTRICULOGRAPHY—A CRITICAL EVALUATION

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For over a third of a century, ventriculography has occupied a well deserved position of importance as a diagnostic tool in the localization of intracranial space-occupying and obstructive lesions. Its success depends upon an adequate demonstration of the ventricular system with a contrast medium, usually negative, instilled directly, cisternally, or by the lumbar route. Room air, oxygen, or helium have been the gaseous agents of choice. It is the purpose of this paper to explore the past record of positive contrast media with an eye to their potential utilization in the present-day diagnostic armamentarium. This seems particularly desirable because of the scant attention the subject has received in this country, despite widespread publications in Europe and Latin America.

HISTORICAL BACKGROUND

The history of positive contrast ventriculography has centered around the search for a suitable substance. Davidoff[7] has emphasized that such a compound must fulfill three criteria, namely: (i) It must provide superior contrast in roentgenography. (ii) It must be innocuous to the patient at the time of injection. (iii) It must be free of long-term deleterious effect.

Lipiodol, an iodized poppy-seed oil, was the first compound employed. In 1923 Sicard and co-workers[19] reported instilling it into the ventricles and watching it descend into the lumbar sac without ill effect. However, it was not until 1928 that adequate ventriculograms were reported by Balado.[3] Two years later, he communicated his additional experience using Lipiodol in 90 cases in efforts to demonstrate the 3rd ventricle, aqueduct and 4th ventricle.[4] He found it superior to negative media and felt that Lipiodol was harmless. In 1935, Lysholm[12] discussed his results using Lipiodol in 114 cases over a 2-year period. He noted that reliance on positive media had diminished as techniques of air studies improved. In addition, he considered Lipiodol undesirable because of very definite irritating properties, especially on the ependyma, if the material were allowed to remain in the ventricles. Furthermore, its high viscosity occasionally worsened the condition of patients with obstructive lesions of the aqueduct, necessitating repeated ventricular taps to relieve the intraventricular pressure. Marcovich *et al.*[14] have reviewed the action of Lipiodol on the leptomeninges and have confirmed its irritating aftereffects in several autopsies.

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Recognizing the limitations of Lipiodol, efforts were made to find a suitable substitute by Antoni,[2] in 1932, with the introduction of Thorotrast (thorium dioxide). The following year Schoenfeld and Freeman[17] reported favorably on their experiences with Thorotrast. Twining and Rowbotham[23] were also optimistic about its possibilities. In 1936, Freeman *et al.*[9] summarized 20 cases in which Thorotrast was used. Despite one death, not necessarily attributable to the Thorotrast, the writers recommended the procedure. However, objections to thorium dioxide were subsequently raised on two counts. Because of its deposition in the cells of the reticuloendothelial system, excretion is limited. Concentrations of this radioactive material were suspected as carcinogenic agents. The ependyma and leptomeninges were also adversely affected. Alexander *et al.*[1] confirmed its role in producing ependymitis. In 1938 Reeves and Stuck[16] likewise demonstrated the severe histologic reaction of the leptomeninges. Unfortunately, the last has not been heard concerning the long-term deleterious effects of Thorotrast. As recently as 1953, Hughes[10] reported a case of aseptic spinal meningitis 13 years after ventriculography. He strongly implicated the Thorotrast employed.

In 1942, clinical trials were conducted using a new contrast medium, Pantopaque (ethyl iodophenylundecylate). It was designed to replace Lipiodol in myelography. According to Steinhausen *et al.*[20] its main advantages lay in its lower viscosity and minimal irritative qualities. Peacher and Robertson[15] confirmed this in a large series of cases. In 1946, Bull[5] began using Pantopaque in ventriculography. Over a 5-year period he employed the substance in 80 cases without ill effect. In spite of widespread utilization of Pantopaque, few reactions were reported. Nevertheless, occasional disturbing cases have been brought to light. Tarlov[22] reported meningeal adhesions in the cauda equina 60 hours after Pantopaque myelography. Mackay[13] has mentioned the occurrence of multiple extra-ocular palsies following cranial extension of Pantopaque from a lumbar myelography. Errors in technique during the instillation of Pantopaque may have accounted for some cases of spinal arachnoiditis. According to Winkelman *et al.*[24] improper cleansing of detergent from syringes or the production of blood at the time of spinal puncture may be responsible for some of the adverse effects attributed to Pantopaque itself. By far the most damaging report is that of Erickson and van Baaren,[8] which cites the history of a patient who died of adhesive arachnoiditis of the basilar cisterns. Pantopaque, from a myelogram 15 months earlier, was clearly shown to be the etiologic agent. How many additional cases of this kind will appear remains to be seen. It merely points up the uncomfortable truth that, despite its universal acceptance, Pantopaque is not innocuous. Consequently, a search for a safer medium is still desirable.

INDICATIONS FOR POSITIVE CONTRAST VENTRICULOGRAPHY

Positive contrast should never be considered a replacement of or an alternative to the standard approach. Gas ventriculography should always be the initial choice and its possibilities utilized to the fullest. To locate the

gas in the desired place requires patience and a willingness to manoeuvre the patient repeatedly if necessary. "Controlled" pneumoencephalography[18] with limited amounts of gas has contributed to improved technique. Even more important has been the increased reliance on laminagraphy to bring out the configuration of small amounts of gas in the aqueduct and 4th ventricle. Nevertheless, there are occasions when it seems impossible to gain the necessary information from a negative contrast medium. Lysholm[12] found this to be the case when there was marked obstruction to flow at the aqueduct or at the outlets of the 4th ventricle. Bull[5] clearly pointed out the difficulties of demonstrating the aqueduct and 4th ventricle when they are decreased in size. In such instances, as little as 0.5 cc. of gas is all that may be routed from the 3rd ventricle caudally, and this may be lost into the basal cisterns before adequate films can be taken. In recent years, patients with intracranial lesions have been seen earlier by specialists when the symptomatology and physical signs are less classical. Gas encephalograms or ventriculograms in such cases may show minimal shifts or incomplete filling of the 4th ventricle. A decision for surgical intervention is then quite difficult. In these instances, confirmation by positive contrast studies is often possible.

TECHNIQUE

There has not been a uniformity of opinion about the various steps necessary to negotiate the passage of the dye from the lateral into the 3rd ventricle. This represents the crucial phase of the procedure. The starting point is always with the dye in the frontal horn of one lateral ventricle. Most writers have injected the dye into one lateral ventricle through a posterior burr hole, which is available when a gas ventriculogram has preceded. The patient is placed in the prone position, which allows the dye to drop immediately into the frontal horn by gravity. By tilting the occiput a little away from the injected side during the instillation of dye, one can avoid placing some of it in the temporal horn. Even if this happens, it is quite easy to manoeuvre it into the frontal horn. Turning the patient supine pools the dye in the occipital horn. Then, with the head dependent, the patient is again turned to the prone position by turning away from the injected side. Stone[21] advocates direct injection of the dye into the frontal horn via a frontal burr hole. Injection of $1\frac{1}{2}$–2 cc. of Pantopaque has yielded very satisfactory films.

The following technique for manipulating the dye has been used with success. It is similar to that employed by Stone[21] and his co-workers. No fluoroscopy is required.

The patient is placed prone on an operating table with one side of the head against a vertical Bucky. After injection, a lateral film is taken to confirm the original position of the dye (Fig. 1a). Then the chin is drawn forward to extend the head. Another lateral film is taken to check the progress of the dye movement. Folded towels or a wooden block under the chin help maintain the position while awaiting the wet film. After complete extension of the head, the dye still may not have passed posteriorly to the foramen of Monro. To facilitate this the table is tipped

in reverse Trendelenburg. At some point, the dye will be seen to drop into the 3rd ventricle on a check lateral film (Fig. 1b). It is important to continue the extension of the head or Trendelenburg slowly until all of the dye is in the 3rd ventricle. This having been accomplished, the patient is turned to the supine position to "trap" the dye in the 3rd ventricle. This is done by moderate extension of the head after the supine position has been attained (Fig. 1c). As can be seen from Fig. 1c, excessive extension may allow the dye to trickle back into the lateral ventricles. Now anteroposterior and lateral films can be taken, which will demonstrate the 3rd ventricle. Finally, the head is flexed slowly to allow the dye to pass into the aqueduct and 4th ventricle (Fig. 1d). Anteroposterior and lateral films are again taken and if visualization is adequate, the patient sits up to allow the dye to pass into the subarachnoid space and thence to the caudal sac for ultimate removal. If the last manoeuvre described above, of flexing the head to visualize the 4th ventricle, is done too quickly, the dye may escape before pictures can be secured.

It is important to emphasize that lateral tilting of the head is not necessary to guide the dye from the lateral ventricle into the 3rd. The reason for this is apparent when one examines a frontal horn in coronal section. Its configuration is such that the inferior portion acts as a wedge-shaped trough wherein the heavy contrast material collects. The foramen of Monro is merely an aperture at the posterior extremity. As the dye passes posteriorly,

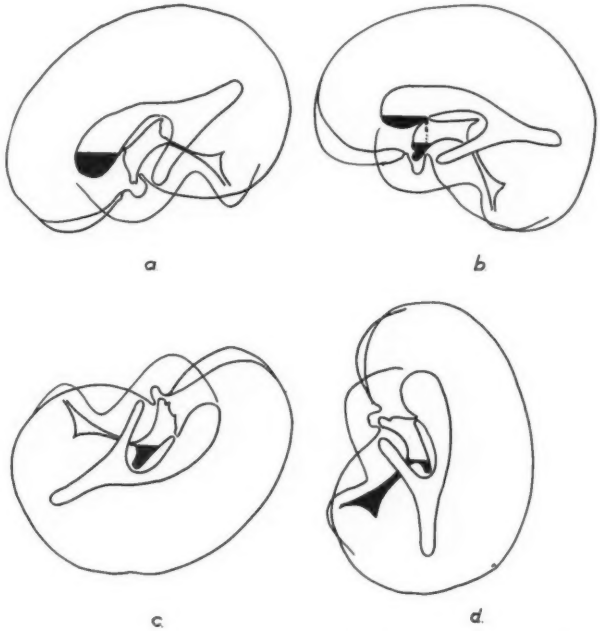

FIG. 1. Schematic representation of location of the dye with various positions of the ventricular system (adapted from Lysholm[12]).

it drops through the foramen by gravity. This method will occasionally fail when the lateral ventricle becomes hugely dilated as in some obstructive process. Then the floor of the frontal horn is converted to a flattened surface, making it difficult to "pool" the dye. In addition, the foramen of Monro then becomes an opening of insignificant size in comparison with the greatly increased floor area of the ventricle.

The alternative method of guiding the dye is to rely on fluoroscopy, as recommended by Lysholm[12] and Bull.[5] In this procedure, the dye is instilled with patient in the sitting position, with the head flexed. The head is inclined slightly against a vertical screen which is on the side opposite the dye. Then, under fluoroscopic guidance, the dye is allowed to pass posteriorly and drop into the 3rd ventricle. Then the procedure is similar to that described above for the remainder of the examination. Carrillo[6] made use of fluoroscopy as a helpful adjunct in particular cases.

Manipulation under fluoroscopy is not as simple as it would appear. The fluoroscopist must be experienced in recognizing the position and course of a small amount of contrast material. Excessive tilting may allow the dye to pass through the interventricular foramen into the opposite lateral ventricle without any dropping into the 3rd ventricle. In addition, many of these patients are too ill to cooperate properly, especially if a gas study has just been done.

The interpretation of positive contrast roentgenograms needs little amplification. The distortion from space-occupying or obstructive lesions is in no wise different from that observed with negative contrast media except that it is much easier to visualize since no superimposed shadows are present to confuse the picture.

ILLUSTRATIVE CASES

Case 1. J.H., a 65-year-old male, was admitted to the Hartford Hospital on Dec. 5, 1955, complaining of difficulty in gait of 6 months' duration. This had been progressive, with veering to either side. For 6 weeks prior to admission he had experienced dull frontal headaches. Nausea and vomiting supervened shortly before admission. A lumbar puncture at another hospital recorded a cerebrospinal fluid pressure of 210 mm. of water; protein was normal.

Examination. The optic discs showed some nasal blurring. Coordination was impaired in the left upper extremity. His gait was ataxic, with a wide base, and tendency to fall in all directions. There was a positive Chaddock's sign on the right.

Laboratory Data. Routine hematology, serology, fasting blood sugar, nonprotein nitrogen and urine were within normal limits. A cephalin flocculation test was negative in 24 hours and 3 plus in 48 hours. A Bromsulphalein test revealed only 9 per cent retention in 45 minutes. Roentgenograms of the chest and skull were negative as was an upper gastro-intestinal series.

Course. On Dec. 7, 1955 ventriculography was performed, using oxygen. The lateral and 3rd ventricles were dilated. However, the aqueduct and 4th ventricle could not be visualized. Consequently, 2 cc. of Pantopaque were injected into the left lateral ventricle and a satisfactory ventriculogram was obtained. The 4th ventricle can be seen to be shifted to the right by a space-occupying mass on the antero-

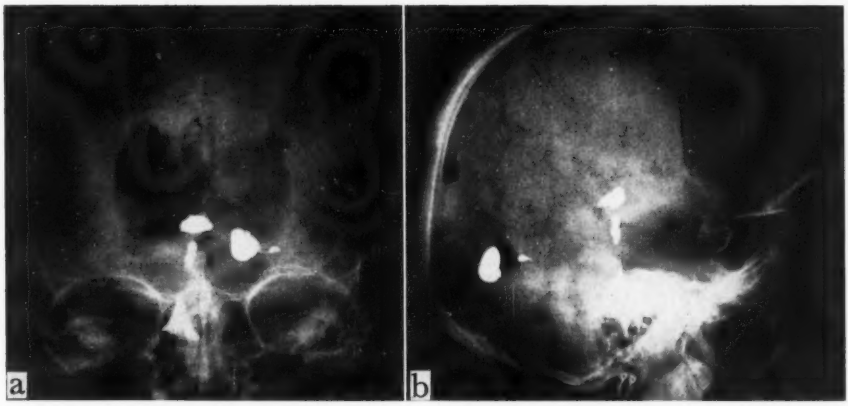

FIG. 2. *Case 1.* (a) Anteroposterior view showing shift to the right of the dye column in the 4th ventricle. (b) Lateral view with suggestion of depression of roof of the 4th ventricle.

posterior projection (Fig. 2a). The lateral view suggests that the mass is in the cerebellum depressing the inferior roof of the 4th ventricle (Fig. 2b).

Operation. The following day, a suboccipital craniectomy was performed (Dr. B. B. Whitcomb). A firm tumor was encountered in the left cerebellar hemisphere which extended to the ependymal surface of the 4th ventricle. The mass was completely removed.

Course. The patient did poorly and died 5 days after operation. Permission for autopsy was not granted.

Pathologic Diagnosis. Metastatic carcinoma, primary site unknown, with pancreas or lung as the likeliest probabilities.

Comment. The patient was quite fatigued following the gas ventriculogram. Consequently it was deemed unwise to attempt to instill oxygen by the lumbar route. The clinical picture alone, though suggestive, was not impressive enough to warrant exploration without radiographic confirmation. There is no reason to believe that the Pantopaque in any way contributed to his ultimate demise. The immediate post-ventriculography period was uneventful.

Case 2. G.D., a 43-year-old married female, was admitted to the Hartford Hospital on Dec. 12, 1955, complaining of severe suboccipital pain on the left of 6 weeks' duration. The pain had progressively increased in severity, with radiation forward, and on admission it was excruciating, accompanied by nausea and vomiting.

Past History. A right radical mastectomy had been performed in 1950 for carcinoma of the breast. In 1953 an ovarian metastatic mass was removed. In May, 1955 a solitary pulmonary metastasis to the lower lobe was removed by lobectomy. Hilar nodes were not involved.

Examination. Evidence of previous surgery was present. No metastases were apparent. There was tenderness on left suboccipital pressure. No other neurological abnormalities were noted.

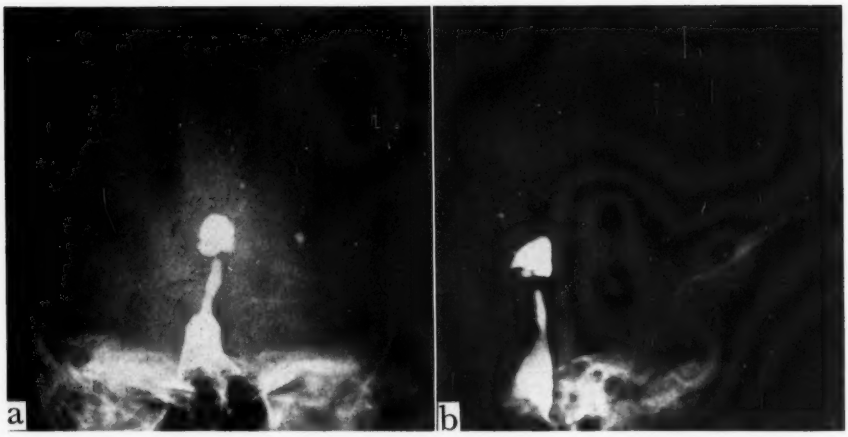

FIG. 3. *Case 2.* (a) Anteroposterior view showing shift of dye column in 4th ventricle to the right. (b) Lateral view.

Laboratory Data. Routine hematology, serology, and urine were within normal limits. Roentgenograms of the skull were normal. Repeat film of the chest showed no evidence of metastases. Lumbar puncture yielded clear fluid with a pressure of 310 mm. of water; no cells were seen; protein was 45 mg. per cent.

Course. Pneumoencephalography with 40 cc. of oxygen was performed on Dec. 14, 1955. Despite laminagrams it was not possible to visualize the 4th ventricle adequately. It gave the appearance of incomplete filling. The lateral ventricles were large. The following day, Pantopaque ventriculography was performed through a left occipital burr hole. A small but definite shift of the 4th ventricle to the right was noted on the anteroposterior film (Fig. 3a).

Operation. A suboccipital craniectomy was performed (Dr. R. H. Dunsmore). With some difficulty a tumor mass was located deep in the left cerebellar hemisphere extending into the cerebellopontine angle. It was completely removed.

Course. Postoperatively the patient did very well and was discharged on Dec. 24, 1955 ambulatory and relatively asymptomatic. A roentgenogram of the lumbosacral spine identified the Pantopaque in the lumbar sac for eventual removal.

Comment. Considering the absence of neurologic signs, a strong suspicion of a metastatic lesion was the only lead in a patient complaining of headache. The elevated spinal fluid pressure could be questioned because of the possibility of inadequate relaxation. Exploration was indicated only with firm radiologic confirmation. Pantopaque was able to provide unequivocal evidence of a space-taking lesion.

Case 3. M.G., a 6-year-old boy, was admitted to the Hartford Hospital on Nov. 20, 1955. For several months his parents had noted staggering gait which was becoming worse. He had a tendency to fall to the left. Six weeks prior to admission intermittent vomiting occurred, especially in the morning. Drooping of the left eyelid was noted. He complained of seeing double when watching television, the images being side by side. Occasional headaches were recorded.

Examination. The patient was an irritable child with a slightly hoarse voice. There was ptosis of the left lid with a small left pupil. The jaw deviated to the left on opening the mouth. There was a right central facial weakness. The left corneal reflex was absent. Coordination tests revealed clumsiness in performing alternate movements of both hands. His gait was ataxic with falling to the left. Deep tendon reflexes were hyperactive in the lower extremities.

Laboratory Data. Routine hematology, serology, and urine were within normal limits. Roentgenograms of the chest and skull were normal. An electroencephalogram showed general dysrhythmia with some depression of activity over the left occiput.

Course. On Nov. 25, 1955 an air ventriculogram was performed. The lateral ventricles and the 3rd ventricle were dilated. The aqueduct appeared displaced in a superior-posterior direction. The 4th ventricle was not demonstrated. Air was injected via the lumbar route and failed to fill the 4th ventricle. Consequently, 2 cc. of Pantopaque were injected through one of the occipital burr holes. The 4th ventricle was demonstrated (Fig. 4a). The measurement from the clivus to the floor of the 4th ventricle was several millimeters beyond the upper limit of normal, confirming the clinical impression of a pontine tumor.

Operation. Because the child's course was one of progressive deterioration, the posterior fossa was explored (Dr. S. J. Silbermann). The cerebellar hemispheres were normal and the 4th ventricle was patent. No definite confirmation of a pontine tumor could be made. Because of the presence of hydrocephalus, a Torkildsen operation was performed.

Postoperatively his course was stormy, complicated by a staphylococcus meningitis and a cerebrospinal fluid fistula. He also experienced a brief episode of gastrointestinal bleeding with tarry stools and transient drop in blood pressure. With the aid of antibiotics and blood his condition stabilized sufficiently to allow efforts at re-appraisal. Because of his general condition, a repeat air study was not done. However, the Pantopaque study was repeated on Dec. 25, 1955 (Fig. 4b), which revealed increased distortion of the 4th ventricle. The tube was removed. After the drainage

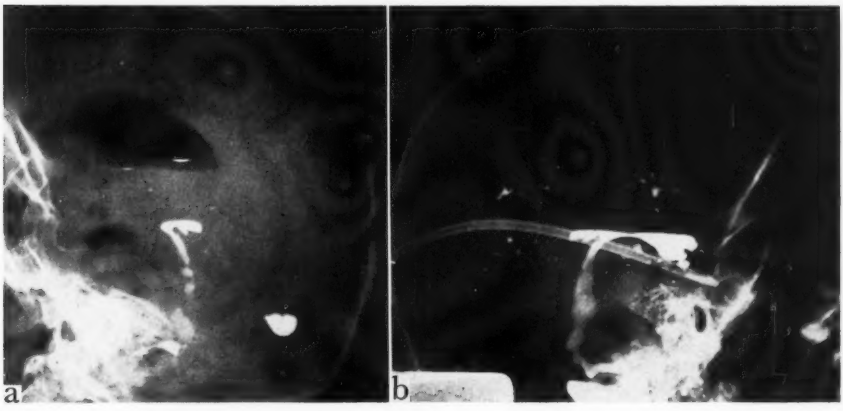

FIG. 4. *Case 3.* (a) Initial Pantopaque study showing pontine tumor. (b) Subsequent demonstration of progression of the lesion.

from the wound ceased, a ventriculoperitoneal shunt was done. The patient still failed to improve and finally expired on March 1, 1956. At autopsy a large cystic tumor, measuring 4 cm. in diameter, was found extending from the lower end of the pons to the cerebral peduncle on the left.

Pathologic Diagnosis. Glioblastoma multiforme.

Comment. As sometimes happens, it was not possible to identify this tumor at operation. However, the two Pantopaque studies confirmed the clinical impression of a brain stem tumor.

Case 4. C.S., a 9-year-old boy, was admitted to the Hartford Hospital on Jan. 8, 1956 with the chief complaint of vomiting and headache of 4 months' duration. Clumsiness had been evident for 2 months, with frequent falls. He also was subject to recurrent attacks of hiccoughing.

Examination. Findings were negative except for bilateral choked discs, more marked on the right.

Laboratory Data. Routine hematology, serology, and urine were normal. Roentgenograms of the skull revealed a beaten-silver appearance and probable diastasis of the coronal suture, both indicative of increased intracranial pressure.

Course. On Jan. 14, 1956 ventriculography with 60 cc. of oxygen was performed. The lateral and 3rd ventricles were dilated. Despite 25 cc. of oxygen injected by the lumbar route the posterior 3rd ventricle was not well demonstrated and no visualization of the aqueduct or 4th ventricle was accomplished. Therefore, 2 cc. of Pantopaque were employed and Fig. 5 shows the posterior 3rd and very beginning of the aqueduct. However, the dye would not flow beyond. The interpretation was aqueductal obstruction caused by atresia or tumor, perhaps extending from the 4th ventricle.

Operation. To rule out the possibility of tumor, a posterior fossa exploration was performed (Dr. B. B. Whitcomb). The cisterna magna was large. The cerebellar hemispheres were normal. There was no tumor of the vermis or within the 4th ventricle. Saline injected into the lateral ventricle trickled through the aqueduct very

FIG. 5. *Case 4.* Obstruction of the aqueduct, probably caused by atresia. Arrow depicts end of dye column at beginning of aqueduct.

FIG. 6. *Case 5.* Filling defect in left side of 4th ventricle caused by medullary lesion.

slowly. A No. 8 rubber catheter was passed through the aqueduct into the 3rd ventricle. This was followed by a gush of fluid through the tube. The cephalic portion of the tube was cut off and left in the aqueduct. Observation after further injections of saline into the lateral ventricle showed much improved flow into the 4th ventricle.

Postoperatively the child has shown steady improvement. One month after operation a pneumoencephalography with 100 cc. of oxygen revealed filling of the entire ventricular system. No additional pathology was demonstrable.

Comment. This apparently is a case of atresia or stenosis of the aqueduct, cause undetermined. The Pantopaque study did rule out a posterior 3rd ventricle tumor and confirmed the suspicion of an obstructive aqueductal lesion. It did not obviate the necessity of exploring the 4th ventricle.

Case 5. J.M., a 40-year-old truck dispatcher, was admitted to Hartford Hospital on Feb. 9, 1956, for evaluation of intractable vomiting. Six weeks previously he began to suffer from recurrent attacks of vertigo associated with burning epigastric pain. A gastro-intestinal work-up at another hospital was negative. His gait became unsteady and persistent vomiting associated with mild headaches supervened.

Examination. There was disturbance of gait, with a tendency to drift to the right. Nystagmus was present on lateral gaze, more marked on looking to the right. Fasciculations of the left side of the tongue were noted.

Laboratory Data. Routine hematology, serology, and urine were normal. Roent-

genograms of skull and chest were normal. Lumbar puncture revealed a normal pressure with clear spinal fluid containing no cells and 61 mg. per cent protein.

Course. On Feb. 15, 1956 pneumoencephalography was attempted but no filling of the ventricular system was achieved. A Pantopaque ventriculogram was done using 2 cc. An irregular defect was shown to persist in the left part of the 4th ventricle (Fig. 6).

Operation. A suboccipital craniectomy was performed (Dr. R. H. Dunsmore). Exploration of the 4th ventricle demonstrated an abnormality in the medulla. The left portion of the floor was pale and elevated. From the obex extending cranially the normal landmarks were lost. The right side of the floor seemed normal but slightly displaced to the right. The abnormal area was punctured with a No. 27 gauge needle. No cyst was encountered. Instead, the underlying tissue had a firm rubbery consistency. It was considered too hazardous to attempt a biopsy.

Postoperatively, the patient's condition was unchanged. Radiation therapy was instituted.

Comment. This lesion was felt by the surgeon to be a tumor of the medulla. After the failure of the pneumoencephalogram, a routine ventriculogram might have yielded the necessary information. However, it was nicely demonstrated with ease using Pantopaque.

DISCUSSION

The cases cited above are fairly representative of the type of pathological entity that can be demonstrated advantageously with Pantopaque. Other authors have diagnosed 3rd ventricle and cerebellopontine angle tumors using this method. What is the explanation for the general neglect of positive contrast ventriculography? There are perhaps three main reasons that come to mind. It seems pertinent to inquire into the validity of each.

(1) The foremost objection is that gas, when properly used, will provide adequate visualization of the entire ventricular system. This has been discussed earlier and need not be repeated. No one would claim 100 per cent success with gas media, so even those with a high number of adequate gas studies might occasionally find a positive contrast medium of help. When laminagraphy is not available, the successes with gas will be considerably reduced.

(2) The risks involved in the use of Pantopaque, the safest positive medium, have been mentioned. It should not be forgotten that occasional mortalities have been attributed directly to gas studies. A high percentage of these deaths have occurred in patients with serious abnormalities such as neoplasms, obstructive processes and vascular disease. Consequently, it is not easy to assess the comparative safety of the two media in the individual case. When faced with imminent surgery on a patient who is deteriorating, the possibility of obtaining additional valuable information would seem to outweigh the long-term risks of Pantopaque arachnoiditis.

(3) Technical difficulty is not a reasonable objection. Experience in many clinics has shown that consistent filling of the ventricular system can be achieved.

CONCLUSION

The history of positive contrast ventriculography has been reviewed, with special reference to various substances employed and techniques of obtaining satisfactory filling. Five representative cases have been reported, using Pantopaque, the safest available substance. This method has been found to be a real asset in the diagnosis of posterior fossa lesions.

Preparation of the drawings by Dr. Robert Lowman is gratefully acknowledged.

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CASE REPORTS

ACOUSTIC NEUROMA WITH MENINGITIS AND SECONDARY COMMUNICATING HYDROCEPHALUS: SUCCESSFUL TREATMENT

REPORT OF CASE

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When acoustic neuromas are permitted to progress through their natural course, death of the patient results from pressure on the brain stem and increased intracranial pressure. The treatment of these tumors is surgical.

In general, three methods of removal have been employed: finger enucleation, intracapsular removal and total extirpation. Avulsion with the finger has been largely abandoned because of excessive mortality. Cushing[1] advocated intracapsular removal of these tumors, and he and others have been able to lower the mortality rate appreciably. Dandy[2] brought total removal into favor and stated that in good hands the mortality should not be any higher than the mortality following removal by the intracapsular procedure. The method of choice would seem to depend on the nature of the lesion and the experience of the surgeon.

While the intracapsular method is considered somewhat safer than total extirpation, it carries a higher morbidity rate. Approximately 30 to 50 per cent of the patients may die of recurrence of the tumor within a 3-year period. The facial nerve, however, can often be spared by this method, whereas in the majority of cases of total extirpation the facial nerve must be sacrificed when the internal auditory meatus is curetted.

The hydrocephalus that is usually associated with acoustic neurinomas is obstructive in type. The aqueduct is distorted, twisted, and finally blocked, resulting in dilatation of the ventricular system above it. In some cases the hydrocephalus may be caused by obstruction of the subarachnoid pathway at the level of the incisura tentorii as the tumor grows through the tentorial notch. Dandy considered hydrocephalus to be the most dangerous complication associated with these tumors.

The following case illustrates some of the complications that can occur with these lesions. However, the hydrocephalus at first was obstructive and later became communicating secondary to purulent meningitis. The case herein reported also illustrates a method of management of complications arising following operation for the removal of tumors of the cerebellopontine angle.

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REPORT OF CASE

A white woman aged 44 years was referred to the Mayo Clinic on Aug. 24, 1954, with the chief complaints of blurring of vision and drainage of cerebrospinal fluid from a suboccipital surgical wound. Both symptoms were of 3 months' duration.

The patient's present illness had begun in March, 1952, with tinnitus and diminution of auditory acuity in the right ear and staggering gait. The symptoms gradually increased in severity, and by July she was having severe headaches in the right occipital region which extended to the right temporal area and were aggravated by lying down. Projectile vomiting occurred and she had one episode of transient diplopia. When she consulted her local physician in July, 1953, she also complained of difficulty in swallowing and regurgitation of fluids into the nasal cavity.

Positive neurologic findings when the patient was examined elsewhere at that time were reported to show diminution of the corneal reflex, moderate peripheral facial weakness and decreased hearing, all on the right side. The movements of the right limbs were slightly in-co-ordinated. The gag reflex was absent bilaterally, and sensation of the right side of the pharynx was decreased. Eye movements disclosed a fine horizontal nystagmus and there was papilledema of both optic disks (3 diopters). No response was obtained to caloric stimulation on the right, while the response on the left was normal. Roentgenograms of the skull, including Stenver's view, were normal. Lumbar puncture revealed an initial pressure of 18 cm. of cerebrospinal fluid and the xanthochromic fluid contained 950 mg. of protein per 100 cc. of fluid. A diagnosis of a right acoustic neuroma was made.

At the first operation elsewhere on July 14, 1953, subtotal intracapsular removal of a right acoustic neurinoma was accomplished through a right suboccipital craniectomy. The wound was drained through a separate stab incision.

The patient's convalescence was satisfactory, but a small leak of cerebrospinal fluid developed at the site of the drain. This was closed easily with several sutures. The patient returned home and did well until June, 1954, when she experienced a sudden blindness.

Re-examination elsewhere was reported to show that the previous operative site was tense and bulging and that the edema of the optic nerve heads had returned. Aspiration of the bulging area yielded clear cerebrospinal fluid. Since this gave relief of the symptoms for approximately 1 week, repeated aspirations were performed.

Subsequent ventriculography revealed dilatation of the third and lateral ventricles, and air was seen to enter the posterior fossa. Little or no air was visualized in the spinal canal or over the cerebral hemispheres. On the basis of the patient's improved status following temporary external ventriculostomy, a shunt leading the cerebrospinal fluid from the posterior cranial fossa into the peritoneal cavity was carried out.

Within several weeks of the time of the cisternal-peritoneal shunt the patient's symptoms recurred, and after several attempts to readjust the shunt it was removed.

Re-exploration elsewhere of the previous suboccipital operative site for the purpose of decompressing the posterior fossa by removing the posterior rim of the foramen magnum and the posterior arch of the atlas was of little benefit. A cerebrospinal-fluid fistula developed through the incision and another stab wound was made into the region to facilitate drainage. The patient was then referred to the Mayo Clinic.

Examination. At the time of admission to the clinic the patient was critically ill and debilitated, and had a bulging cystic mass in the right suboccipital region with three separate musculocutaneous ostia which leaked cerebrospinal fluid. On one occasion a white odorless exudate was noted from the central opening. The right cornea was anesthetic, and the facial muscles and the soft palate on the right side were weak. There was in-co-ordination of the limbs on the same side. Conjugate gaze to the right was paralyzed, and weakness of the lateral rectus muscles was noted. Chronic papilledema of 2 diopters was present bilaterally. On the basis of these findings, it was felt that the tumor had recurred and, despite the great risk involved, re-exploration of the right cerebellopontine angle was advised.

Operation. After several days of antibiotic therapy, the old operative incision was reopened

with the patient under local anesthesia. Through tedious and careful dissection a total removal of a typical acoustic neuroma from the right angle was accomplished. The tumor was approximately 3.5 cm. in diameter and weighed 30 gm.

The *histologic picture* was that of an acoustic neuroma.

The *postoperative course* was stormy. On the third day the wound was tense and hemorrhagic cerebrospinal fluid escaped under pressure. External ventriculostomy was instituted in an attempt to control the increased intracranial pressure, and thus permit healing of the wound. This was, however, only partially successful, and the wound continued to drain intermittently.

Despite massive doses of antibiotics, Streptococcus faecalis and Aerobacter aerogenes were cultured from the wound drainage, the ventricular fluid, and the lumbar spinal fluid.

On Sept. 3, 1954, the ventricular-fluid culture revealed Streptococcus faecalis. This organism was sensitive to penicillin, 5 units per ml., and tetracycline, 1.5 μg. per ml. This infection had developed regardless of the fact that 1,000,000 units of penicillin had been administered prophylactically daily from Aug. 26 to Sept. 9, 1954. When it became apparent that an infection in the cerebrospinal fluid caused by Streptococcus faecalis had developed, the therapy was changed. Penicillin was given in doses of 20,000,000 to 30,000,000 units daily by the intravenous route combined with 1 gm. of dihydrostreptomycin twice a day. However, cultures of the cerebrospinal fluid continued to be positive for Streptococcus faecalis, and from Sept. 11 to 13, 1954, 10,000 units of penicillin combined with 50 mg. of dihydrostreptomycin were given intraventricularly through an indwelling catheter.

At this time Streptococcus faecalis disappeared, but unfortunately it was replaced by Aerobacter aerogenes. In other words, one serious infection produced by a partially resistant organism had been controlled, only to have it replaced by a more formidable one.

During this period of transition the patient was afebrile for 3 days. Following this, the temperature was never less than 100°F. with frequent spikes to 103° or 104°. Aerobacter aerogenes was cultured from the cerebrospinal fluid on at least 10 different days. The sensitivity of this organism was reported as follows: Tetracycline, more than 6.2 μg. per ml.; streptomycin, more than 25 μg. per ml. Although this organism was resistant to tetracycline and to streptomycin separately, a trial of the combination of these two substances seemed indicated, since it is known that resistant gram-negative organisms will respond occasionally to this combination of antibiotics. Unfortunately, in this patient the cultures of the cerebrospinal fluid continued to grow Aerobacter aerogenes, and the temperature remained elevated.

Further sensitivity tests indicated that this organism was sensitive to chloramphenicol, 6.2 μg. per ml., and polymyxin, 1.5 μg. per ml. Administration of chloramphenicol alone was started in oral doses of 500 μg. every 4 hours on Oct. 5, 1954, but since it failed to control the infections, 25 mg. of polymyxin every 6 hours intramuscularly was added on October 11. On October 14, the temperature dropped to normal for the first time in about a month, and on the same day the last positive culture was reported.

A program of daily spinal puncture had been initiated in the attempt to reduce the cerebrospinal-fluid pressure and allow healing of the wound. At the time of each lumbar puncture the bulging suboccipital wound would become soft and flattened, indicating a communication.

An indwelling spinal ureteral catheter was then inserted into the lumbar subarachnoid pathways to provide continuous drainage of the cerebrospinal fluid.[5]

By the 7th postoperative week, somewhat previous to the sterilization of the cerebrospinal fluid with antibiotic therapy mentioned in previous paragraphs, the wound in the suboccipital region on the right and the ostia of the cutaneous sinuses had healed completely.

The patient was then afebrile and her wounds healed. She still, however, was suffering from a postinflammatory communicating hydrocephalus. On Oct. 23, 1954, a subarachnoid-omental shunt was achieved by inserting a large polyethylene tube into the lumbar subarachnoid space and placing the other end in the lesser omental bursa in order to relieve the communicating hydrocephalus.[3,4]

One week later, with the patient under local anesthesia, a right spinofacial anastomosis[6,7]

was done to correct the facial palsy incurred during the total removal of the tumor. The patient was able to be dismissed in good condition 11 weeks after her original admission. It has recently been reported that she was still in good condition more than a year after her dismissal.

COMMENT

The case presented is interesting because it illustrates the successful management of some of the complications that can be associated with acoustic tumors. The meningitis and subsequent hydrocephalus of communicating type were undoubtedly the result of the cerebrospinal-fluid fistulas, which had been present for several months.

The relief obtained from the continuous lumbar spinal drainage and the failure of the patient to absorb the fluid without external egress necessitated a shunting procedure to some depot outside of the nervous system. Since the fluid was infected, it could not be shunted into a body cavity without threat of secondary infection in the recipient area or blockage of the tube. An external type of shunt was considered. A ventriculomastoidostomy shunt was considered inadvisable, since the patient had partial paralysis of the right vagus nerve and risked aspiration of the infected fluid into the lungs. Subarachnoid-ureterostomy with or without nephrectomy was deemed inadvisable in the patient's debilitated condition because of the electrolyte loss that may be associated with this shunt. The final choice was to insert a ureteral catheter into the lumbar subarachnoid space as a temporary measure until antibiotic therapy could sterilize the cerebrospinal fluid. Sterilization was achieved after several weeks and it was then possible to make a permanent shunt using the omental bursa as the receptacle as described by Dodge and ReMine.[4] This allowed for resorption of the cerebrospinal fluid with relief of the communicating hydrocephalus without upsetting the bodily economy through electrolyte imbalance in this debilitated patient.

ADDENDUM

When this paper was submitted to the Editors of the *Journal of Neurosurgery*, Dr. Paul Bucy called our attention to a very similar experience that he had had. He was kind enough to supply us with a report of his case which is added.

A 41-year-old right-handed white woman presented herself at The Chicago Memorial Hospital in 1949 with symptoms of a left cerebellopontine angle tumor. At this time an acoustic neuroma was completely removed, sacrificing the facial nerve. The immediate postoperative period was uneventful, and 1 month later a left facial-spinal accessory anastomosis was made. The patient continued to improve, returning to her job as a dressmaker. Her face was symmetrical at rest, and she could effect a smile by attempting to elevate her left shoulder.

In May, 1954, she returned, complaining of headaches and dizziness, but after a brief period these subsided.

In September, 1954, nausea and vomiting developed. Examination revealed a papilledema and bulging of the left suboccipital operative site. Her gait was quite unsteady, and there was ataxia of the left extremities, which seemed more severe than it had been. There was nystagmus on looking to either side, more marked and coarser on looking to the left than to the right.

On Sept. 20, 1954, the left cerebellopontine region was re-explored. The dura mater had reformed. On opening it we came upon a large cystic cavity occupying the lateral part of the posterior fossa. It was lined with a pearly gray membrane similar to the new dural membrane. The cavity had no opening by which it communicated with any other space. When the medial wall of this cavity was removed we passed through a thin layer of degenerated cerebellar tissue into a large cavity which proved to be a deformed fourth ventricle. Choroid plexus

could be seen in its roof posteriorly. Methylene blue injected into the left lateral ventricle promptly appeared in the fourth ventricle. There was no evidence of a recurrence of the tumor. As we had now demonstrated that there was free ventricular communication and as we had connected the cystic cavity with the ventricular system, it seemed wisest to stop in the hope that this would relieve her symptoms.

Microscopic examination of the tissue removed at operation revealed scarred nervous tissue lining the cystic cavity.

The patient's symptoms and signs persisted, and on Sept. 27, 1954, a third ventriculostomy was made. On Oct. 16, 1954, she was discharged, asymptomatic except for minimal left cerebellar signs. The surgical craniectomy site was soft and flat. The patient was re-admitted Nov. 28, 1954, with a 2 to 3 weeks' history of headaches, nausea and vomiting, and somnolence. The suboccipital operative site was bulging and tense. For this reason on Nov. 29, 1954, a right ventriculosalpingostomy was completed; and again her complaints remitted and she was discharged on Dec. 21, 1954. Thereafter she did well and gained 5 pounds in weight.

She returned Feb. 10, 1955, because of recurrent and persistent headaches, nausea and vomiting, which had been present for 1 week. At this time a saline irrigation of the polyethylene tube demonstrated an obstruction distally in its intra-abdominal portion. The obstruction was overcome by gentle irrigation. A ventriculogram made at this time showed a symmetrically dilated lateral ventricular system. The patient was discharged on Feb. 17, 1955.

On May 1, 1955, she again returned with symptoms of intracranial hypertension which began 2 weeks earlier. Repeated saline irrigation of the shunt failed to relieve the obstruction, and the posterior fossa was explored on May 9, 1955, through a midline incision. The dura mater was incised in a cruciate manner to expose the cerebellar midline and cerebellar hemispheres. The cerebellar hemispheres showed no evidence whatsoever of herniation, and, in fact, the cisterna magna was quite large. Once the arachnoid overlying the cisterna magna was opened, cerebrospinal fluid poured out copiously. By gentle retraction the fourth ventricle was readily visualized, and it was observed that adequate cerebrospinal fluid was coming down from above. Immediately underlying the right cerebellar tonsil and between the cerebellum and the brain stem was a small aneurysm (3 mm. in diameter) on one of the minor blood vessels. It was removed and appeared to be a purely incidental finding. A small amount of indigo carmine was then introduced into the left lateral ventricle through the brain cannula, and the dye was seen to flow promptly through the fourth ventricle.

Postoperatively, the patient was not relieved of her intracranial hypertension, ventricular punctures being necessary to relieve pressure, and on May 12, 1955, dye injected into the right ventricle was recovered from the lumbar sac in about 15 minutes. Because of these findings, on May 14, 1955, a spinal subarachnoid right ureterostomy was effected. The patient was discharged asymptomatic and ambulatory on June 4, 1955. The suboccipital craniectomy sites were flat. The patient has remained well since.

The reason for the sudden development of a communicating hydrocephalus in this case, 5 years after the original tumor was removed, has never been clear.

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PAPILLOMA OF THE CHOROID PLEXUS OF THE LATERAL VENTRICLES CAUSING HYDROCEPHALUS IN AN INFANT

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Papillomas of the choroid plexus may cause hydrocephalus by excessive production of cerebrospinal fluid though impressive clinical evidence in support of this concept has been meager. A unique case is presented here in which bilateral papillomas of the choroid plexus of the lateral ventricles were found in association with communicating hydrocephalus caused by overproduction of cerebrospinal fluid. The sequence of events in the management of the condition leading up to its recognition took a devious course which provides evidence of a kind not previously reported.

CASE REPORT

A female child, aged 2½ months, was admitted to the New York Hospital on Feb. 15, 1954.

History. The baby was born spontaneously after a full term normal pregnancy at another hospital on Nov. 29, 1953, and weighed 7 lbs. 10 oz. She was thought to have a somewhat enlarged head at the time of birth. Several cyanotic episodes occurred during the first few weeks of life, but otherwise she fed and cried normally. At 1 month of age the head measured 41 cm. in circumference and the chest 39.5 cm.

Examination. She was a well-nourished infant with a vigorous cry. There was obvious hydrocephalus. She could not hold up her head, which measured 45.5 cm. in circumference and showed prominent parietal bossing. The anterior fontanelle measured 6×7 cm. and was tense and bulging. There were cracked-pot resonance to percussion, convergent strabismus and horizontal nystagmus.

Subdural taps were negative. On ventricular tap clear, colorless fluid was obtained. Phenolsulfonphthalein injected in a lateral ventricle was promptly recovered from the opposite lateral ventricle and the lumbar subarachnoid space. Approximately 60 cc. of fluid were removed and replaced with air. Roentgenograms disclosed dilated ventricles and a cortical thickness of 3 cm. The protein content of the ventricular fluid was 13 mg. per cent.

The condition was regarded as a communicating hydrocephalus. Pyelography demonstrated the presence of two normally functioning kidneys.

1st Operation, Feb. 20, 1954. A right nephrectomy was performed, followed by a lumbar subarachnoid-ureteral shunt with a polyethylene tube.

Course. The baby tolerated the procedure well, but on the 3rd postoperative day she rapidly became dehydrated and went into shock. An immediate forced infusion of saline corrected the state, but over the next few days it became apparent that she was losing an excessive amount of electrolytes and water via the ureteral shunt. The addition of salt to the diet, plus the administration of large quantities of intravenous fluids, was necessary to prevent dehydration. Daily infusions of 500 to 1000 cc. of half normal saline were administered together with oral feedings. Each time an attempt was made to discontinue intravenous clyses or when they were given too slowly serious dehydration often bordering on shock occurred. In all, about ten such episodes took place in a period of 2 months. Chemical determinations during these episodes generally showed moderately low serum CO_2, normal chloride, slightly low to normal sodium and high potassium. All attempts to maintain adequate hydration by means other than daily infusions containing large quantities of salt met with failure. After 8 weeks of this therapy it was evident that no adjustment to the continued excessive fluid loss had occurred.

2nd Operation, April 20, 1954. The subarachnoid-ureteral shunt was transplanted to the peritoneal cavity in the hope that the fluid would be re-absorbed.

Course. The day after this procedure enormous abdominal distension occurred accompanied by vomiting and again the startling picture of dehydration. Over the next week, however, the clinical condition improved. The abdominal distension decreased somewhat, the appetite increased to a point far beyond what it had been and the anterior fontanelle remained soft. The baby was soon able to get along on oral feedings alone. There was no accurate estimation of fluid output during this period except that in the nurses' records it is noted that daily diaper changes averaged 10 per day while the ureteral shunt was functioning, and only 6 per day after it was placed in the peritoneal cavity.

FIG. 1. Appearance of the child at age of 1 year. Note the enlarged head and abdomen 7 months after a spinal subarachnoid-peritoneal shunt.

The child was discharged 10 weeks after admission.

2nd Admission. Six weeks later the patient again entered the hospital because the polyethylene tube had become plugged with resulting sudden increase in intracranial pressure and size of head.

3rd Operation, June 11, 1954. A new tube was promptly inserted and a satisfactory recovery from the procedure took place.

3rd Admission. On Nov. 18, 1954, at the age of 1 year, the baby was readmitted because of slowly progressive abdominal enlargement. This condition had persisted since the last discharge and had reached the point where ascites had become a more critical problem than the hydrocephalus (Fig. 1). The head now measured 48 cm. and the abdomen 67 cm. in circumference.

Course. An abdominal paracentesis was performed to relieve the child's respiratory distress and improve her appetite; 3250 cc. of clear colorless fluid with a chloride content of 108 mg. per cent were obtained. On the day after the paracentesis another episode of shock from dehydration appeared and was corrected over a 24-hour period with 2100 cc. of parenteral fluids besides regular oral feedings. The child gained 1600 gm. in this period and the abdomen quickly refilled despite a tight abdominal binder.

When her condition had once again become stabilized after the paracentesis it was thought that the only therapeutic measure left was cauterization of the choroid plexus.

4th Operation, Oct. 29, 1954. A small right parieto-occipital craniotomy was performed and the right lateral ventricle was opened. In the region of the glomus of the choroid plexus was a multicystic globular mass. Implanted in numerous places in the walls of the cysts were pink buds of choroidal tissue. The cystic fluid was thin, clear and colorless. The portions of the choroid plexus that extended anteriorly in the temporal horn and body of the ventricle were large meaty looking processes having only occasional small cystic elements. That part of the choroid plexus at the margin of the foramen of Monro appeared normal. The entire tumor was removed, and measured 7 cm. in length by 3 cm. in its widest diameter (Fig. 2).

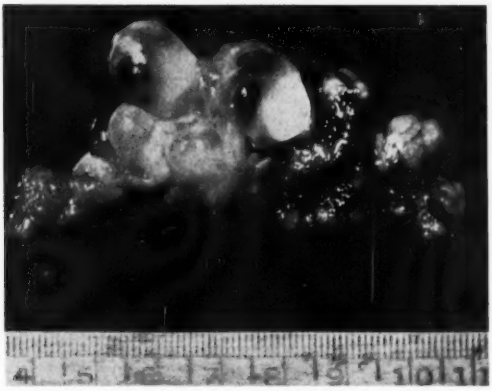

FIG. 2. Photograph of tumor removed from the right lateral ventricle.

Course. Except for a persistent collection of fluid under the scalp the baby made a satisfactory recovery from the operation. There was no appreciable change in the degree of ascites, but some degree of overhydration occurred when parenteral fluids were given in amounts similar to those used before the operation.

5th Operation. On the 12th day after removal of the right ventricular tumor a similar surgical procedure was performed on the left side. A multicystic tumor of the choroid plexus similar to that in the opposite ventricle was excised. Just before closure of the wound, however, the child went into shock and expired on the operating table despite resuscitative measures.

Pathological Examination. Both papillomas (Figs. 3 and 4) revealed multicystic and papillary proliferation with no evidence of malignancy. There were masses of villous and frond-like structures. These usually possessed a stalk composed of a few strands of connective tissue and contained an engorged blood vessel lined by endothelium. The papillary processes were covered by acidophilic cuboidal cells containing rounded dark- and light-staining nuclei. There were no mitotic figures or pleomorphism. The cysts were lined by a single layer of cuboidal cells similar to but smaller than those in the villi.

Autopsy. There was a massive subarachnoid hemorrhagic clot extending over the basilar and temporal areas of the brain. This was the apparent cause of death. There was no blood in the ventricles and the source of the bleeding could not be determined. The choroid plexuses were absent in the lateral ventricles; those that remained were normal in appearance. The for-

FIG. 3. Low-power photomicrograph of the tumor. There are frond-like processes of the choroid plexus and many cysts of variable size.

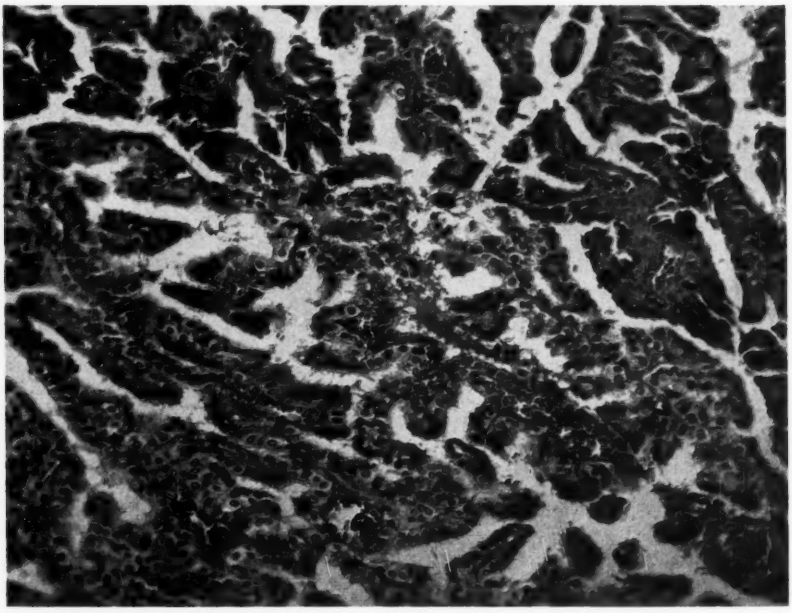

FIG. 4. High-power photomicrograph of the tumor. The histologic appearance is that of normal choroid plexus without evidence of malignancy.

amina of Monro, the aqueduct of Sylvius and the foramina of Luschka and Magendie were patent. The ependyma and basilar meninges were normal grossly and microscopically except for a slight degree of ependymitis at the juncture of the aqueduct and 4th ventricle.

The abdomen was greatly distended and the peritoneal cavity contained about 3,000 cc. of clear faintly yellow fluid. The polyethylene tube leading from the spinal subarachnoid space lay free in the peritoneal cavity, and was patent. The peritoneal surfaces were smooth and glistening, and the intestines were normal in appearance and position. The liver, spleen, biliary system, pancreas, kidney, adrenals, pelvic viscera and blood vessels appeared normal. The liver weighed 280 gm. and the spleen 26 gm. which are average for this age; they were of normal consistency and appearance on cut sections. Microscopic sections of the various abdominal organs showed essentially normal tissues. In brief there was no intra-abdominal disease to account for the large collection of fluid in the peritoneal cavity.

DISCUSSION

In the neighborhood of 100 papillomas (and angiomas) of the choroid plexuses have been reported in the literature. At least 10 per cent occurred in infants in the first year of life[2] and the majority were accompanied by hydrocephalus. It is commonly accepted that cerebrospinal fluid is formed by the choroid plexuses and *a priori* reasoning readily leads to the conclusion that a papilloma of the structure, which in most cases is nothing more than a benign overgrowth, produces hydrocephalus by oversecretion. However, papillomas in the 4th ventricle may produce a de-

gree of ventricular obstruction which has made conclusions tenuous regarding the origin of hydrocephalus in these cases. In the cases of papillomas in the lateral ventricles Dorothy Russell[6] appropriately raised a question of the possibility of accompanying ependymitis or basal meningitis as a cause of the hydrocephalus. When it is realized that intraventricular hemorrhage, xanthochromia or elevation of the protein content of ventricular fluid have been frequent findings in the reported cases it is to be expected that at least microscopic evidence of reaction in the ependyma and leptomeninges should be common.

More conclusive proof that papillomas of the choroid plexus may cause hydrocephalus has been dependent on actually determining an excessive production of cerebrospinal fluid or by demonstrating a cure of hydrocephalus by surgical excision of the abnormal plexuses.

In Fehr's[1] 23-year-old patient with a papilloma of the choroid plexus in the 4th ventricle the removal of 200 to 300 cc. of spinal fluid daily failed to produce more than transient diminution in the increased cerebrospinal fluid pressure. Kahn and Luros,[3] and Matson[5] each reported subsidence of increased cerebrospinal fluid pressures and apparent cure after excision of papillomas in the lateral ventricles (Kahn and Luros' patient was 20 years old and Matson's was 4 weeks old). McGuire, Greenwood and Newton[4] reported an apparent cure of hydrocephalus in a 3-month-old infant by excision of a bilateral angioma of the choroid plexus which in its microscopic description is not unlike what others have called papilloma.

In the case reported here the unfortunate operative death prevented concluding that the hydrocephalus was cured by excision of the tumors though it seems likely that such would have been the case had the child survived. However, the overproduction of cerebrospinal fluid is demonstrated beyond doubt, first, by the excessive loss of fluid through the ureteral shunt and second, by the development of massive ascites when the spinal subarachnoid shunt was transferred to the peritoneal cavity.

The failure to recognize the tumors in the beginning resulted from the use of an inadequate amount of air in performing the ventriculography. Also, the normal ventricular fluid gave no clue to the presence of the lesions. The failure to recognize earlier the significance of the excessive loss of spinal fluid through the ureter and into the peritoneal cavity is explained by the lack of previous experience of this kind.

SUMMARY AND CONCLUSIONS

This report presents the evidence for concluding that hydrocephalus resulted from the presence of benign papillomas of the choroid plexus in the lateral ventricles of an infant.

In the belief that the condition was a communicating hydrocephalus a spinal subarachnoid-ureteral shunt and later a peritoneal shunt was performed, each of which resulted in excessive loss of cerebrospinal fluid.

The lesson to be drawn is that it must be kept in mind that occasionally a papilloma (or an angioma) of the choroid plexus may be the cause of hydrocephalus. Suspicion of presence of the lesion should be raised by the finding of xanthochromia or excessive protein in the ventricular fluid, though these changes are not constant. Excessive loss of fluid through a ureteral shunt or the development of ascites with a peritoneal shunt should strongly suggest the presence of a tumor of the choroid plexus.

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NOTICES

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Examinations were given by the American Board of Neurological Surgery in St. Louis, Missouri, May 2–5, 1956, and the following were certified:

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HARVEY CUSHING SOCIETY

The 24th annual meeting of the Harvey Cushing Society was held in Honolulu, Hawaii, April 16–18, 1956. The following officers were elected: President, Leo M. Davidoff, New York; President-Elect, Howard A. Brown, San Francisco; Vice-President, W. Gayle Crutchfield, Charlottesville; Secretary, David L. Reeves, Santa Barbara; Treasurer, Hendrik J. Svien, Rochester, Minn.; Historian, Louise Eisenhardt, New Haven; Member of Executive Committee, Frederic Schreiber, Detroit. William T. Peyton, Minneapolis, was appointed as member of the American Board of Neurological Surgery. The following were appointed to the Membership Committee: George S. Baker, Rochester, Minn., Edmund J. Morrissey, San Francisco, Frank P. Smith, Rochester, N. Y. Mrs. John E. Webster, Detroit, is President of the Ladies Auxiliary, and Mrs. Eben Alexander, Jr., Winston-Salem, is President-Elect.

* Certified in October 1955 in New Haven, Connecticut.

SIR HUGH CAIRNS

The Society of British Neurological Surgeons has decided to commemorate the name and work of the late Sir Hugh Cairns. The memorial will take the form, in part, of a lecture to be given in London or Oxford from time to time by eminent men whatever their country. For this it is necessary to provide an endowment fund to cover an honorarium and traveling expenses.

The Society, knowing of the high esteem in which Sir Hugh Cairns was held by his many friends in this country and abroad, believes that these might wish to express their admiration for his achievements by subscribing to this memorial. The magnificent work done by Sir Hugh Cairns in organizing, with the warm cooperation of the Army authorities, the special neurosurgical skills to be applied immediately behind the battle marked a lasting advance in military surgery. Subscriptions should be sent to the Honorary Treasurer of the Society of British Neurological Surgeons, Mr. J. B. Pennybacker, The Radcliffe Infirmary, Oxford.

PAN-PACIFIC SURGICAL ASSOCIATION

The 7th Congress of the Pan-Pacific Surgical Association will be held in Honolulu, Hawaii, November 14–22, 1957. All members of the profession are cordially invited to attend and are urged to make arrangements as soon as possible if they wish to be assured of adequate facilities.

An outstanding scientific program by leading surgeons with sessions in all divisions of surgery and related fields promises to be of interest to all doctors.

Further information and brochures may be obtained by writing to Dr. F. J. Pinkerton, Director General of the Pan-Pacific Surgical Association, Room 230, Young Building, Honolulu, Hawaii.

SCANDINAVIAN NEUROSURGICAL SOCIETY

The 12th annual meeting of the Scandinavian Neurosurgical Society will be held in Århus, Denmark on August 31 and September 1, 1956.

Members of the local Department of Neurosurgery will read papers on acute vascular cerebral accidents, encephalitis associated with choked discs, hormonal disturbances in chromophobe adenoma of the pituitary gland, treatment of acute traumatic brain-stem lesions, and indications and prognosis in surgical treatment of protrusion of lumbar intervertebral discs.

Any inquiries should be sent to Professor R. Malmros, Århus Kommunehospital, Denmark.

JOURNAL OF NEUROSURGERY

The *Journal of Neurosurgery* is devoted to the publication of work relating primarily to neurosurgery, including studies in clinical neurophysiology, organic neurology, ophthalmology, radiology and pathology. Short articles on unusual cases and on technique, special instruments or equipment that might be useful to others in the field are also acceptable.

MANUSCRIPTS should be addressed to Dr. Louise Eisenhardt, 333 Cedar Street, New Haven 11, Conn., U.S.A. They should be typewritten in double space, with tabular matter and passages for small print on separate sheets. All materials should be mailed flat.

REFERENCES should be arranged alphabetically and cited by superior numerals in the text. The following order should be used:

Articles: Name of author, full title of article, name of periodical, year, volume, first and last page of article. Abbrevations of names of periodicals should conform to the style used in *A world list of scientific periodicals published in the years 1900–1933* (Oxford University Press, 1934).

Books: Name of author, full title of book, city, publisher, year, edition, full pagination (if book is in more than one volume, give the number of volumes).

ILLUSTRATIONS. Care should be taken not to use too many illustrations, since the Journal provides no figures free of charge. Color plates also are inserted at the expense of the contributor. If illustrations are larger than 8.5×11 inches, reduced glossy prints should be submitted instead.

SPECIAL TYPOGRAPHY. Tables and also text set up in small print in excess of 10 per cent of composition costs are charged to the author.

PROOF CORRECTIONS will be allowed without charge up to 5 per cent of the original cost of composition. The cost of changes in page proof, if made by the author, will be borne by him. *Page proof* will be submitted to authors only when special questions arise.

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SUBSCRIPTIONS. The subscription rate for the volume of six bi-monthly issues is $11.00 in the United States and Pan-American Union; $11.50 in Canada; $12.00 in other countries. Single copies are $2.00 postpaid. Single copies of Volume VIII, Number 1, January 1951 issue: A Symposium on Intracranial Vascular Abnormalities: $3.00 postpaid, if available. Volume I, Number 1 is supplied only on orders for the complete volume. Payments may be made in advance to Charles C Thomas Publisher, 301–327 East Lawrence Avenue, Springfield, Illinois, U.S.A.

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